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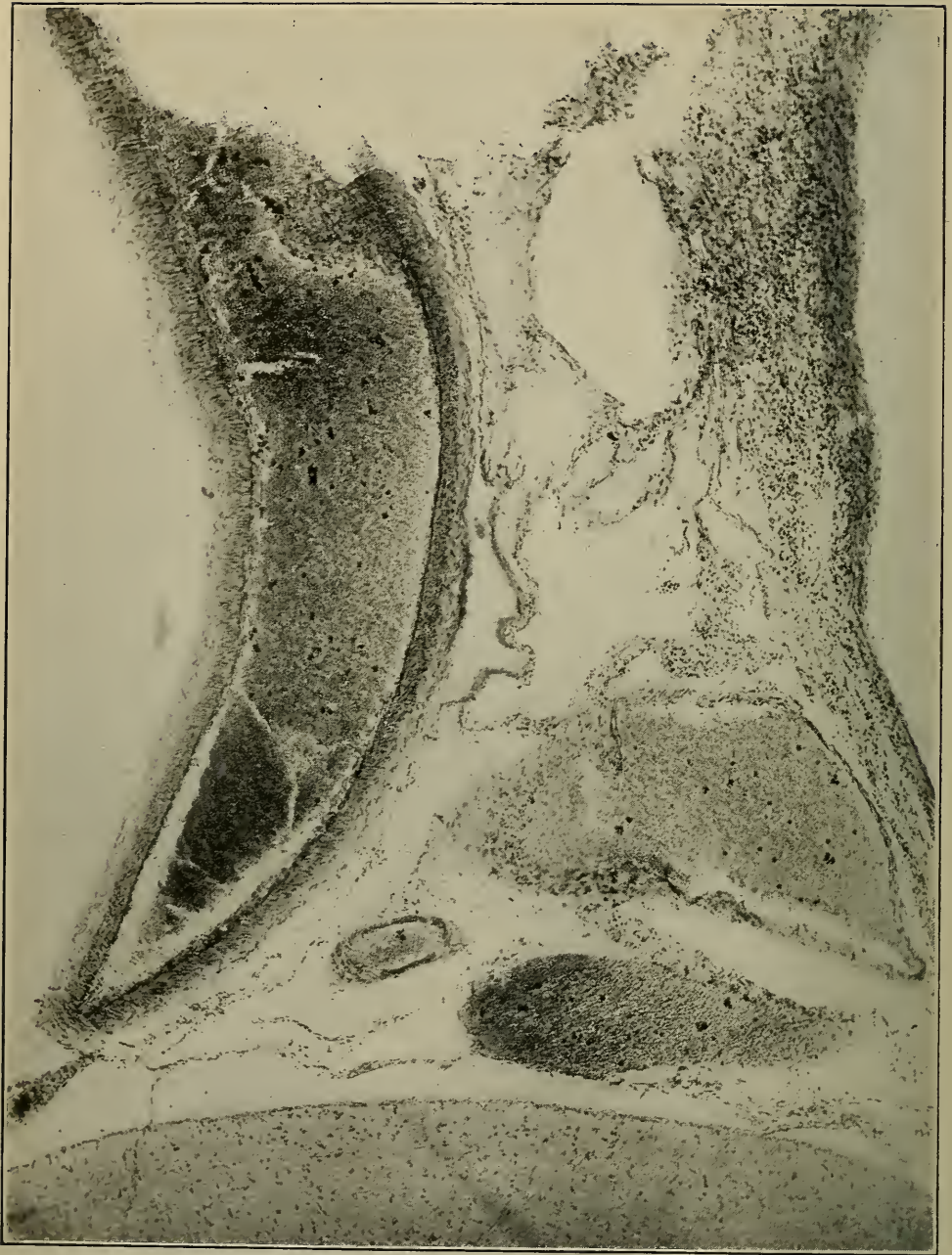
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ACUTE EPIDEMIC ENCEPHALITIS

RECAP

*An Investigation by The Association for
Research in Nervous and Mental Diseases*



Frontispiece

Human brain. Mononuclear cell infiltration and congestion of vessels in meninges of cerebrum in acute epidemic encephalitis.

ACUTE EPIDEMIC ENCEPHALITIS

[LETHARGIC ENCEPHALITIS]

*An Investigation by The Association for
Research in Nervous and Mental Diseases*

REPORT OF THE PAPERS AND DISCUSSIONS AT THE
MEETING OF THE ASSOCIATION; NEW YORK CITY,
DECEMBER 28TH AND 29TH, 1920

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PREFACE

DURING the preparation of this volume for publication there was considerable discussion by members of the Publication Committee as to the best way of presenting the material which it contains. It was felt that a formal report of papers and transactions of the society would be less readable than the present form of presentation. In preparing the material the endeavor was made to harmonize two conflicting aims. It was felt that each contributor should be credited with all the facts which he had established, and at the same time it was thought unwise to include duplicate reports of work by different investigators. As a result, the Committee found it necessary to publish only such material submitted by a given contributor as had not already been submitted by another. This naturally led to the deletion of parts of contributions. It should be appreciated by both contributors and readers that this was done solely in order to avoid duplication of material, and not because of lack of excellence of any parts of the contributions received.

A further object of the Publication Committee has been to allow no contribution, either in the written report of investigators or brought out in discussion, to go unrecorded. For this reason all questions of clinical bearing submitted by the Committee and answered by contributors, are included in the text.

The Committee wishes to take this occasion to express its thanks to contributors to the volume for the detailed and painstaking studies which they have made and reported in their abstracts. In preparing the material for publication the members of the Organization and Programme Committees of the Association, after going over the various articles, recommended the above outline of publication to the

President. This outline the President approved, and thereupon assigned the various sections to different members of these Committees for editing. In succeeding volumes it may be found desirable to alter or modify this mode of presentation. In the case of this volume, blame for certain of its failures or praise for what excellence it may possess in the way of presentation should be distributed among the various members of these Committees of the Association.

P. B.

NEW YORK,
September, 1921.

INTRODUCTION¹

A NEW organized effort, a new association, operating along untried lines, has been suggested to you in the belief that it might have as a result the scientific advance of neurology and psychiatry.

From the outset the proposal met with your hearty endorsement; you have brushed aside the misgivings which, nowadays, assail all of us when anything to add to our labors is proposed; you have done this in the belief that what we are going to do now will bring substantial return to our science.

Those of us who conceived and nurtured the idea wish, first of all, to express gratitude for your immediate and hearty support. Time will show, we believe, that your faith has not been misplaced, and that the new association will bring us into closer relationship, always in the interest of our life's work.

The present era of turmoil exerts its baneful disintegrative influence upon all educational and scientific advance. If in medical research this debasement were limited to a diminution of output, the matter would be of no special concern, for it would allow time for a criticism and assimilation of much that had been presented heretofore. But unfortunately, the deficiency does not show itself in lack of production; for never before were there as many medical journals as at the present time; never before were the mail boxes of medical editors more crowded; and it must be added, the scientific value of the articles offered seems to be in inverse ratio to their number. The amount of necessary reading entailed

¹ Presidential address by Dr. Walter Timme delivered at the opening of the first meeting of the Association for Research in Nervous and Mental Diseases, New York, December 28, 1920.

by this enormous output in a vast number of scattered publications becomes a serious matter, even if only as concerns time. Time expenditures can be made only out of a limited capital, of which inevitable subtractions make a rapidly diminishing fund. The burning question of the times is the intensive use of the minute. How shall we economize our time-energy unit? And then, how shall we best use it?

Specialization has seemed to solve partially our problem. But more and more is the realization driven home that specialization, far from becoming narrower must be planned in accordance with its obligations to medical science as a whole, and not exclusively to the clinic and laboratory. It must consider not only itself but also the sociological and industrial conditions of our environment. Thus viewed, specialization becomes universalization. In no field is this more in evidence than in neurology and psychiatry.

The neurology of a few years ago was content and complacent with a bald diagnosis of some disease,—let us say, for example, lead polyneuritis. The diagnosis with its prescribed treatment was all there was to it. But it is now glaringly evident that we owe a duty to the community, commensurate with that which has brought about compulsory vaccination. This duty requires us to define, in the first place, the safeguards to be erected for the protection of our fellows; we must interest ourselves further and inquire, Why should lead have singled out this particular individual? Is it a matter with him of less resistance to that particular poison, carelessness in its use, or both. Are other co-workers similarly affected or likely to be? What methods are provided by the plant to protect the workers? Are they adequate? Is there supervision? Does the state take cognizance of laxity in the enforcement of proper laws for the safety of lead workers in all plants, and are there proper state laws to insure safety to lead workers? What is the loss to the community of an improperly regulated industry? The answer to these questions implies an active and widespread investiga-

tion undertaken to improve medico-sociological conditions. In England, for instance, Sir Thomas Oliver has accomplished results in this particular field that make him a public benefactor. We cannot escape our responsibility here.

Our psychiatry would be poor indeed if, for example, it stopped with the discovery that the cause of paresis is syphilis. It is its duty to go into the sociological problems involved in the dissemination of syphilis and attempt to solve them. These problems are apparent and need not particularly be detailed now. The point I desire to make is that our specialization must be of universal application.

In practically all our work a similar situation exists. Multitudinous problems confront us. The time element, the energy factor, the bread and butter necessity—to say nothing of the opposition that is always encountered—are almost beyond encompassment. Shall we deny the responsibility? We cannot. Ours is the problem; ours as well must be the quest for the solution. The largest factors in the solution are the energy and time elements.

I think you will agree with me that much that we do as individuals in our chosen field is opportunistic. By this I mean that if in the course of our work an interesting case, or a series of such, arises or an apparently new symptom is discovered, or a new method of enquiry suggests itself, we make a memorandum, and, when time allows, we expand upon it and publish a paper. Such publications fill the medical journals. They are discrete, non-related, not properly balanced, all too often redundant and verbose; many are mere duplications and some few are reliable. There is a multiplicity of single, uncritical clinical observations to one of well-founded merit. And the number of theories of disease advanced on the flimsiest of groundwork makes the reading of medical journals much like attendance upon the moving picture: logical sequence is thrown to the winds so long as weird contrasts and rapidity of change dominate the story. But we have a ready excuse. When our work shows incoordination of thought and plan, limitation of scope, slight and

uncertain conclusions, and, as a result we are accused of superficiality, we usually fall back upon the statement that medicine in America cannot properly advance until our clinical observations and deductions are checked up, and more post-mortem material is made available. In spite of the truth which such an apology holds, I believe our position would be better if we decried less our lack of such opportunity, and bent our energy more to intensive ante-mortem study. One thing we Americans possess, and that is a vigorous initiative for combined effort. Let us make application of this quality to our present problems. Such combination of effort, to be successful, requires several conditions: First, a goal to be attained; second, a coordination of the forces available; third, a proper supervision and control to prevent overlapping or undermanning. If these factors can be furnished, results will follow; there will be concerted, coordinate action by a group of men on a definite problem without loss of time or duplication of work. It will reduce the amount of reading necessary while enhancing the interest; there will be one story in several chapters, with a conclusion.

It is in accordance with these principles that our present Association for Research in Nervous and Mental Diseases was founded.

Let us understand at the outset that this Association is not merely one more society added to innumerable others for the bedevilment of the medical fraternity. It is congenitally different and will functionate in a manner quite its own. The discussions with their tergiversations incidental to large meetings will retire before sounder methods of getting at truth.

To outline briefly the functions of the organization which we have brought into being, to declare its aims and purposes, and to show that by its existence many of the evils before enumerated and which automatically are increasing, will be lessened or eradicated, is my chief function today.

Foremost of all, the coordination of efforts in one direction, following a plan outlined in advance with a definite

object in view is the main principle underlying our proposed activities. A group of men of experience in neurology and psychiatry elected by the members of the Association, after due and mature deliberation, decide upon an object of research—some disease entity—which has ever balked and baffled us. The choice of the subject is made one or possibly two years in advance of the date set for its intensive discussion and workers in all fields of medicine are urged to engage in the investigation in their own special lines. Laboratory workers, pathologists, physiologists and clinicians set to work along definite paths, each group in its own way attacking the problem. The material for them to study is furnished by all physicians of the Association and by others interested, and due credit is given for such assistance. In this way, practically all cases of the disease in the territory covered by the Association will come under the observation of those studying the problem. At once the multitudinous, incoordinated, single observations which fill our medical journals become superfluous; redundancy and reduplication fade away. What otherwise would have taken years to accomplish by the most painstaking efforts and collaboration becomes a matter of a few months. When, finally, the day for a casting up of results of this coordinated and intensive study arrives, the papers embodying the results of the individual researches are carefully studied by the members of the Commission; and when presented to the Association by them, the proponents of the various theses are interrogated as to their work, their conclusions, and on any details that may still need elucidation. At the conclusion of the meeting, the Commission will prepare for publication all the matter presented to it in coordinated, sequential form, together with its own comments as a commission, and issue a volume to be distributed to the members of the Association. Each of us will then be in possession of all that is known about the disease in question to the last minute, almost up to the "time of going to press." In a comparatively short period of time, a series of such volumes will constitute American

archives of our specialty of surpassing completeness. Research thereafter will need to begin only with the latest American archives on the subject, and the weary task of looking up the literature, which is as far as many intrepid but time-limited souls get, will be a thing of a revered past.

You should know that the plan of the organization was evolved only by the very assiduous constructive work of the members of the various organization committees, who gave generously of their time and advice during the past year and without whose initiative and support there could have arisen no such association as ours. I violate no confidence in stating that the brunt of the work and responsibility fell upon our devoted friends, Drs. Charles L. Dana, Frederick Tilney and Foster Kennedy, and that whatever merit there may be found is due in the largest part to them.

I believe that little analysis will be necessary to demonstrate the enormous advantage accruing to all of us, and to neuropsychiatric science in particular, by the application of the methods, the trial of which begins today. There will, doubtless, be many faults uncovered; many changes in procedure will become necessary before a fairly perfected plan will come out of it all; but with your kindly cooperation and constructive criticism, I see arising out of this modest beginning a powerful force for good, a unified and inspired all-American group of neurologists and psychiatrists, whose basic aim is the advance of American Medicine.

CHAPTER I

GENERAL AND HISTORICAL CONSIDERATIONS, INCIDENCE, ETIOLOGY AND PATHOGENESIS

THIS first chapter deals with certain general considerations of epidemic encephalitis. The general characteristics of the lesions and the extent of our most recent knowledge of the disease are discussed by Dr. Lewellys F. Barker of Baltimore. Dr. Shirley W. Wynne, of the Health Department of New York City, has made a contribution to its epidemiology, making use of the data available to the Health Department. Dr. Israel S. Wechsler has collected statistical data from hospital reports, reports of physicians and other sources, covering both this country and Canada.

A summary of the observations of Dr. William M. Thalheimer of Milwaukee, Dr. Leo Loewe and Dr. Israel Strauss of New York City on pathogenesis concludes the reports of this chapter. A more detailed report in reference to pathogenesis, including animal experimentation, is presented by these writers, as well as by several others, in Chapter VII of this volume.

GENERAL CONSIDERATIONS (LEWELLYS F. BARKER). Since von Economo in 1917 described as "lethargic encephalitis" an epidemic disease in which the diagnostic criteria consisted of the triad—somnolence, ophthalmoplegia, and profound asthenia, our knowledge of the symptomatology and pathology of acute, subacute and chronic non-suppurative inflammations of the nervous system has undergone rapid and prodigious augmentation. The spread of the disease in epidemic form over the whole civilized world and the occurrence of successive outbreaks in modified

form in each of several countries have given an unusual opportunity to clinical and pathological investigators for the exact study of this remarkable malady under the most different conditions. It is but little wonder that progress has been made by leaps and by bounds; and though we are still ignorant of a vast deal that we should like to know, the conceptions of the disease held today are very far removed from those of 1917. A great variety of states, which at that time would not have been classified under the rubric of this disease, are now immediately recognized as belonging there by all familiar with the malady and the bibliography.

The number and the variety of symptoms which may be presented by patients suffering from this infection, and the diverse combinations and sequences of the symptoms in single cases, are striking features of the disease. A French writer, C. Achard, has well expressed it, "the disease is polymorphous and acyclic." It occurs in an endless number of clinical forms, and though in most cases the course of the malady is divisible into several stages, the serial sequence of these stages may be very different in different epidemics and even in single cases in the same epidemic. The variegated symptomatology, the great diversity of syndromes met with, the apparent absence of any constant chronology in the development of the syndromes, and the aping by this malady of almost every well-known and well-defined neurological symptom-complex, have been responsible for many mistakes in diagnosis and have caused even some of the best-informed students of the disease almost to despair of creating any sort of order out of the clinical chaos presented.

That there is, however, a fundamental unity in this perplexing diversity, we are now fairly certain. We have to deal with a single disease, due doubtless to a specific virus, in which the clinical manifestations are very diverse, owing to differences in intensity of the virus and its toxins and to variations in the localization of the multiple lesions produced. The epidemic character of the malady, a prevalence so wide that an acquaintance with it has become possible to

all consulting internists, neurologists and ophthalmologists, as well as to large numbers of other general and special practitioners, the characteristic pathological histology of the widely disseminated lesions in the nervous system, the combinations and overlappings in certain cases of two or more syndromes that are often met with singly in others, have placed beyond doubt the fact that we, despite the multiplicity of symptoms, are dealing with a unitary disease dependent for its causation upon some specific infectious agent.

EPIDEMIOLOGY (SHIRLEY W. WYNNE). Our knowledge of the epidemiology of encephalitis is very meager, but it may serve a useful purpose if we briefly set forth those facts which we possess. It is agreed that it is an acute disease; that it affects the nervous system, and that its outstanding symptom is lethargy. It occurs in epidemic form, and most observers are agreed that during the last two hundred years we have had several epidemics of this disease. Crookshank, in a very interesting article in the *Boston Medical and Surgical Journal*,¹ attempts to trace the disease back to the time of Hippocrates. He calls attention to the fact that during the last four hundred and fifty years there have been a number of epidemics of the disease in many countries of Europe, but that in these epidemics there is apparently a confusion of encephalitis, poliomyelitis and influenza. The one outstanding fact in Crookshank's history of this disease which, as he tells us, was described under different names and attributed to different causes, in the different countries in which it occurred, is that the diseases which he thinks were encephalitis, poliomyelitis and influenza bore a resemblance in their symptomatology and occurred more or less simultaneously.

There was in 1712 a well-defined outbreak of sleeping sickness in Germany, which was attributed to the eating of poisonous food, and it is interesting to note that food poisoning was again advanced as the cause of this disease in the last epidemic. The present epidemic started in Vienna in the

¹ Crookshank, F. G. A note on the history of epidemic encephalomyelitis. *Boston M. & S. J.*, January 8, 1920, clxxxii, 34.

winter of 1916 and 1917. In 1918 it appeared in England and its greatest incidence was in the spring of that year. In March, 1919, the first cases appeared in New York, at least these were the first to be officially reported to the Health Department. From that time until the present, cases have occurred from day to day. During 1919 there were 46 deaths reported from this disease in New York City. During the first eleven months of 1920 there have been 228

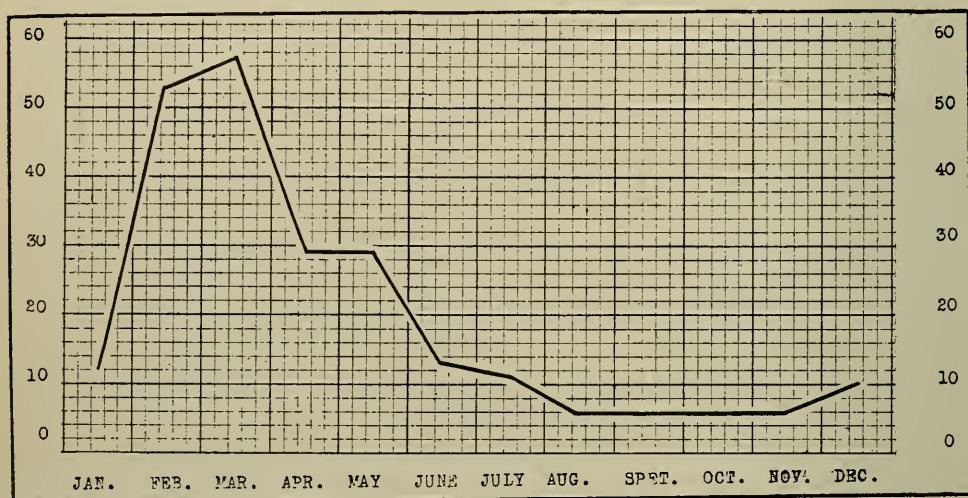


FIG. 1. Monthly mortality, 1920, in City of New York.

deaths reported. In January, 1920, there were 12 deaths; in February, 53; in March, 57; in April, 29; May, 30; June, 13; July, 11; and after that the rate fell to 6 deaths a month during the remaining months until the first of December. The deaths were distributed throughout all the boroughs of the city, the largest number of cases being reported, of course, from the most populous boroughs.

The Public Health Reports show cases reported from California, from Florida and from Maine, during the same week, denoting a widespread distribution. But we have been unable to trace any definite path that the epidemic followed, as we did in the epidemic of influenza.

Three theories have been advanced as to the cause of the

disease during the last year and a half: (1) That it was due to food poisoning, a theory quickly disproved. (2) That it is a mutated form of influenza. Some still cling to this idea and advance as the reason for this theory the fact that both diseases occurred about the same time. (3) That encephalitis and influenza were very widespread, and roughly followed the same course in traveling from one country to another, the proponents of this theory also stating that influenza has in different phases of the same epidemic affected different tissues of the body: thus at one time the respiratory tract, at another the gastro-intestinal tract, and at still another the nervous system. There has also been a striking similarity in the age distribution of encephalitis and influenza.

On the other hand, the epidemic of encephalitis started in Vienna in the winter of 1916 and 1917, before the outbreak of influenza had made its appearance. In England the time of the epidemics of encephalitis and of influenza more nearly coincide. In the United States the epidemic of encephalitis has followed more closely the epidemic of influenza. Furthermore, in none of the series of cases that has been studied have we been able to secure a sufficiently large number of histories of previous attacks of influenza or of exposure to influenza to justify the belief that there was any connection between the two diseases. Dr. Louis I. Harris, of the New York Health Department, studied 63 cases, and of these 16 gave a history of a previous attack of influenza, 14 gave a definite history of exposure to influenza, and 40 gave no history of a previous attack or of exposure to influenza. In the 3 remaining cases the histories were unsatisfactory and were disregarded. Similarly, in 117 cases of encephalitis there were but 17 cases which gave a history of influenza. Our experience during the last epidemic was that there were multiple or secondary cases of influenza in almost every family where encephalitis occurred. So far reported, there has been only one instance where there has been a secondary case of encephalitis lethargica. Indeed, in going over the report of the Committee that studied the epidemic in Eng-

land, there is related the case of a boy whom they observed sleeping in the same bed with four other children of the family. The boy died, but none of the other children had the disease or showed any symptoms of it. This would seem to indicate that there was no relation—no direct relation—between encephalitis and influenza. The influenza epidemic or pandemic, as Flexner states, perhaps served only to prepare the soil for the epidemic of encephalitis by lowering the resistance of the communities invaded.

As to *poliomyelitis*, it has been said that this disease was similar to encephalitis and was caused by the same agent, because both diseases attack the central nervous system, both occur in epidemic form, and because, as some authors have attempted to point out—Crookshank notably—there was a chronological relation between the epidemics of poliomyelitis and encephalitis. On the other hand, there are many differences in the epidemiology of the two diseases. Encephalitis is distributed throughout all age groups. Cases have been found in children under one year of age and in persons over seventy-five years of age. The greatest incidence, however, is during adult life, particularly between the ages of twenty-five and forty-five. Poliomyelitis, on the other hand, is found for the most part among children, and during the epidemic of 1916 in New York City over 90 per cent of the cases of poliomyelitis occurred among children under ten years of age.

The seasonal occurrence of the two diseases also differs. Encephalitis occurs in all seasons of the year. Deaths were reported during every month of 1920 up to December 1st, but the greatest incidence was in February and March. Poliomyelitis, on the other hand, occurs most frequently in warm weather. Another point is that if both diseases were due to the same organism, we should expect to find frank cases of poliomyelitis during epidemics of encephalitis and vice versa. This has not been the case. [The Committee appointed to study the disease in England observed in certain communities the occurrence of encephalitis where no

cases of poliomyelitis were reported, and the occurrence of poliomyelitis where no cases of encephalitis were reported. In the largest centers of population, cases of both diseases were found simultaneously, but that is true of almost all the acute contagious diseases. In New York City we have cases of diphtheria, scarlet fever, and measles occurring at the same time.

The following questions submitted to Dr. Wynne before the Commission, together with the answers to them, are here reported *verbatim*.

DR. WILLIAMS: Have you studied the bacteriology of alleged cases of influenza preceding or in contact with cases subsequently shown to be encephalitis of specific etiology?

DR. WYNNE: No sir.

DR. WILLIAMS: Are you satisfied that many alleged influenza cases are not abortive encephalitis forms first?

DR. WYNNE: I think they are not. I don't think it is within the province of our office to pass on that; it is a question of diagnosis.

DR. DANA: How correct do you suppose is the diagnosis of deaths from encephalitis? You say you had 200 odd cases in 1920. Do you suppose most of the diagnoses are correct?

DR. WYNNE: That is a rather difficult question to answer. You realize what difficulty the statistical office has in determining whether the causes of death reported are reliable. In this instance we have checked up a number of diagnoses by sending out our diagnostician, and I think that the large proportion of these deaths have been true cases of encephalitis. Furthermore, the majority of these deaths have been reported from hospitals where the opportunities for diagnosing them correctly have been greatest. We have not had many cases reported in general practice from private homes.

DR. DANA: How does the mortality rate compare with that in other cities in this country? Chicago and Philadelphia?

DR. WYNNE: I have been unable to get any information along that line. I referred to the Public Health Service as the quickest means, and they informed me that the records are far from complete. The cases have not been reported promptly but have been

scattered throughout the year, so that I am unable to answer that question at this time.

DR. SKOOG: Have you a record of verification by autopsy of the fatal cases?

DR. WYNNE: There was no way of getting that on the short time I was given to prepare this little paper, because the method of tabulating in statistical offices does not show on the tabulating card the fact that the diagnosis has been verified by autopsy or other methods. It would require a return to the original method and taking the matter up with the physician who reported the case.

DR. PATRICK: May I ask Dr. Wynne how, as he expresses it, the influenza prepares the soil for encephalitis if there is no direct relation?

DR. WYNNE: Rather by weakening the resistance of the persons in the community which has been invaded by an epidemic.

DR. PATRICK: That would be assuming that their resistance has been diminished although they have not had influenza.

DR. WYNNE: I realize there is a school that adheres to the belief that the susceptibility of the individual has nothing to do with the infection; that it is due entirely to the virulence of the infecting organism. On the other hand, while we are awaiting positive proof of such a theory, I think most epidemiologists are agreed that other diseases, especially epidemic diseases, will lower the resistance of the persons in the community to another epidemic disease, and it was on that ground that I made that remark. I find in going over the literature that Flexner felt the same way about it.

DR. PATRICK: I don't know if I get the point of your reply or if you get the point of my question, but I gather from your statements that in cases of encephalitis, influenza has not preceded it in the individual. How then does it follow that influenza prepares the soil if the individuals who acquire epidemic encephalitis have not had influenza?

DR. WYNNE: Simply by lowering the resistance of all the people in the community. Where there may have been some cases not reported, they simply served as a means of passing it along to the others who came down with the disease.

DR. PATRICK: Do you think that these encephalitis cases should be reportable as a disease?

DR. WYNNE: That is a question which it is not fair to ask me to answer.

A MEMBER: What is your total percentage of mortality?

DR. WYNNE: Among the cases studied the mortality was 40 per cent. We have no way of knowing the mortality rate for the entire city.

DR. SACHS: Isn't it true, Dr. Wynne, that at the time of an epidemic the diagnosis of the disease is apt to be made just as often in cases not really definitely established?

DR. WYNNE: I think that is true of such widespread conditions as influenza, and undoubtedly during the influenza epidemic we had deaths reported that were probably not from influenza; but in a disease where we have only 228 deaths in an entire year out of a population of six millions, and where most of the deaths have occurred in institutions, I think it is safe to say that the percentage of error in those 228 deaths is small.

DR. STRAUSS: Have you not noticed that both in the epidemics of 1918-1919 and 1919-1920 as the epidemic of influenza waned the epidemic of encephalitis began to reach its height?

DR. WYNNE: The first phase of the influenza epidemic was in the spring of 1918; the second heavy phase was in the fall of 1918. In the spring of 1919 our first cases of deaths from encephalitis were reported. During that year, however, there were only 46 deaths from encephalitis reported in the city. During January, 1920, there were less than 20, in February there were 54, and in March there were over 50 deaths reported from this disease, and then it began to wane after that until the last month when there were but 6 deaths reported. Hence, it is true that the influenza epidemic waned before the cases of encephalitis appeared in this country, or in this city at any rate. Abroad, I believe, the cases of encephalitis antedated those of influenza. In France and England the period more nearly coincided.

DR. TAYLOR: Are there any statistics available regarding distribution as to social position,—that people living in salubrious surroundings are less liable?

DR. WYNNE: Apparently not. There are no definite statistics along those lines, but judging from distribution by nationalities and occupations in the city, there seems to be little difference.

DR. KENNEDY: Dr. Wynne, your death-rate seemed very high. Is it not possible that the death-rate seems higher to a public

board of health who are looking at marked cases, cases which are very severe, in which the death incidence would be higher?

DR. WYNNE: Those cases in that group were of the severe type. The milder cases had not been reported, and therefore were not investigated.

DR. KENNEDY: It is our belief that 40 per cent is rather high; I think there were a good many minor cases which were not reported and which didn't come under your view.

DR. WYNNE: Yes, we had to depend upon the voluntary reports of physicians to send us in the questionnaire.

INCIDENCE (ISRAEL S. WECHSLER). The statistical data of 864 case reports were studied. Practically every part of the United States, as well as Montreal, Canada, is represented, although more than half of the records came from New York City. Cases from clinics and dispensaries were purposely omitted, since many of them had previously been seen in hospitals. The discrepancy in the various totals is due to the fact that in a few instances the necessary data were left out in the records submitted.

Age. The youngest cases on record are in infants of four weeks. There were 3 such cases. One occurred in an infant of six weeks and 1 in one of seven weeks. The oldest case recorded is that of a man of eighty-four. Evidently no age was spared, although the greatest number occurred between twenty and fifty. To those who have sought to correlate epidemic encephalitis with poliomyelitis this fact is of some importance. If the percentages in the various decades were compared with the percentages of the population of the various decades it will be seen that childhood was practically spared and even adolescence was not much affected.

TABLE I
AGE INCIDENCE

	Below 5	6-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	Total
No.	13	37	136	222	215	140	72	23	6	864
Per Cent.	1.5	4	15.7	25.7	25	16.2	8.3	2.8	.7	100

Sex. The male sex was affected much more severely than the female. There were 522 males and 342 females—a percentage of 60.5 to 39.5 or a ratio of almost exactly 3 to 2. This is difficult to explain. Greater exposure of the male sex or occupational strain may possibly be held to account, but the suggestion is merely speculative. The fact itself, however, is sufficiently interesting and worthy of note.

Occupation. Every conceivable occupation was represented among the cases. There are seventeen physicians in the group, almost 2 per cent of the total number of cases. When one considers that the total number of physicians of the country is slightly over $1/8$ of 1 per cent of the whole population, the incidence among doctors was exceptionally high, or almost 16 times as frequent as among the average population. Whether this fact has any bearing on exposure or infectivity can merely be conjectured. Among the physicians were two hospital interns.

Nativity. Of 860 cases reported upon there were 387 natives and 473 foreign born, that is 45 per cent of the former and 55 per cent of the latter. The native population of the country in general and even that of New York City exceeds greatly the foreign population and yet the disease incidence was greater in the latter. This fact is difficult to explain even when one takes into consideration the high incidence of disease among adults who furnish the bulk of the foreign population, and the fact that most of the cases here recorded came from New York City.

Civil Status. There were 300, or 34.7 per cent, single patients, 491, or 56.9 per cent, married and 73, or 8.4 per cent, not stated. This preponderance of the married over the single may perhaps be explained by the fact that most of the cases (about 65 per cent) occurred in persons over twenty-five years of age.

Pregnancy. There are records of twenty-two pregnant women who had encephalitis. Two of these aborted and one had a cæsarian section done. One woman was delivered in the eighth month of pregnancy, both mother and child

TABLE II
COMPOSITE STATISTICS

Age	Sex	Occupation	Nativity	Civil Status	Mortality	Other Facts
Below 5	Males	Practically every conceivable occupation	U. S.	Married	Died 178 or 21%	Pregnancies 22
13..... 1.5%	522 or 60.5%		387 or 45%	491 or 56.9%		
6-10	Females		Foreign	Single	Recovered, improved or Chronic 672 or 79%	Familial incidence 5 instances of 2 in one family and 2 doubtful cases
37..... 4.0%	342 or 39.5%		473 or 55%	300 or 34.7%		
11-20				Not stated		
136..... 15.7%				73 or 8.4%		
21-30						
222..... 25.7%	864		860	864	850	
31-40						
215..... 25.0%						
41-50						
140..... 16.2%						
51-60						
72..... 8.3%						
61-70						
23..... 2.8%						
Over 70						
6..... 0.7%						
864						
100.0%						
Total						

CLASSIFICATION			
No.	Form	Per Cent	No.
303	Lethargic.....	35	16
129	Parkinsonian.....	15	11
89	Bulbopontine.....	10.3	8
66	Psychotic, Delirious Toxic-infectious.....	7.8	7
55	Midbrain and Basal ganglia.....	6.3	5
44	Myoclonic.....	5	4
43	Athetoid and Choreic.....	5	4
29	Radicular, Neuritic, Neuralgic.....	3.3	3
24	Meningitic.....	2.8	2
18	Hemiplegic.....	2.1	1
	Myelitic, Spastic.....		1
	Hemorrhagic.....		1
	Convulsive.....		1
	Cerebellar, Ataxic.....		1
	Paraplegic.....		1
	Thalamic.....		1
	Catatonic.....		1
	Apoplectic.....		1
	Anterior Poliomyelitic.....		1
	Posterior Poliomyelitic.....		1
	Tabetic.....		1
	Pseudobulbar.....		1
	Optic Atrophy.....		1

surviving, but no mention is made whether the child showed any lethargic symptoms. Four deaths are recorded. It is interesting to compare the low mortality in these patients with the extremely high mortality of influenza in pregnancy. The question of the influence of encephalitis on the offspring is of even greater interest, but is rather difficult to answer at present.

Familial Incidence. In only five instances, a little over one-half of 1 per cent, did the disease occur in two members of one family. There were two other instances, but both are doubtful and one of them occurred in a servant of the house. Considering the rarity of the instances one may well look upon them as accidental; and in view of the practical absence of contagion in hospital cases (two interns did contract the disease), one may consider the fact of direct transmission as almost negligible.

Clinical Forms and Anatomical Localizations. The great variety of clinical forms or types which were encountered, make a uniform classification very difficult, if not impossible. The nomenclature varied with many observers, which added to the difficulty. Some divided, subdivided and classified their cases by creating types for every noticeable departure from the general picture, while others grouped them all under one or two heads. The anatomical substratum furnished justification for the former, whereas clinical and etiological considerations guided the latter.

The following questions submitted to Dr. Wechsler before the Commission, together with the answers to them, are here reported *verbatim*.

DR. BARKER: I would like to ask if the incidence among physicians could be due to the fact that all of the cases were recognized by most of them. They would know where to go to get a diagnosis in the first place, whereas large numbers of the general population perhaps don't recognize it. Would that be a possible explanation?

DR. WECHSLER: I do not know if that would be a warranted assumption. Most of the men reported on all the cases. It is a fact that struck me as exceptional.

PATHOGENESIS (LEO LOEWE and ISRAEL STRAUSS). Berkefeld filtrates of brain material, nasopharyngeal mucous membrane and nasal washings from cases of epidemic encephalitis have produced in rabbits and monkeys lesions typical of this disease. Spinal fluid and blood of cases have also produced the disease experimentally in these animals. Many of these animals have succumbed with the typical picture of epidemic encephalitis. The virus has been passed through many series of animals. It can be preserved for many months in 50 per cent glycerol.

Cultures made on ordinary mediums and by Rosenow's technique have proved negative.

By means of the ascitic-tissue culture methods perfected by Noguchi a minute, filtrable organism from cases of epidemic encephalitis has been cultivated, using brain, nasopharyngeal mucous membrane, nasopharyngeal washings, spinal fluid and blood.

This same organism has been recovered from the brain and nasopharyngeal mucous membrane of animals that have been inoculated with virus, and with cultures which have succumbed to the experimental disease. The cultures recovered from these animals have produced the disease when injected into other animals and the organism has again been isolated. Positive animal inoculations have been obtained with the 15th generation of this organism. It has been established that the organism survives contact with 50 per cent glycerol for several days, and, providing strict anaerobic conditions are maintained, remains viable in individual cultures as long as twelve months.

Isolated colonies of the organism in the solid Noguchi medium have been picked and successful subinoculations secured in fluid medium. These fluid cultures have also produced encephalitis in animals.

Results indicate that epidemic encephalitis can be differentiated from epidemic poliomyelitis for the following reasons: Rabbits are susceptible to infectious material from epidemic encephalitis and not from poliomyelitis. Monkeys

are very susceptible to poliomyelitis and relatively refractory to material from epidemic encephalitis. Spinal fluid from poliomyelitis cases is innocuous when injected into rabbits and monkeys, whereas spinal fluid from cases of epidemic encephalitis produces typical lesions of the disease in both of these animals.

Control studies have been uniformly negative with material obtained from patients suffering from or dead of conditions other than epidemic encephalitis.

Further work done by Loewe and Strauss since their last publication in the *Journal of Infectious Diseases* (1920, xxvii, 250), affords them additional data for affirming the conclusions just cited. They have had occasion to subject to animal inoculation and culture additional infectious material, such as brain, nasal washings and cerebrospinal fluid from encephalitis cases. A tabulation reveals that their experimental evidence has been adduced from a study of the following human material: 26 brains, 18 nasopharyngeal mucous membranes, 29 nasopharyngeal washings, 40 spinal punctures, and blood from 4 cases. In the course of their experiments to date they have utilized some 640 monkeys and more than 600 rabbits.

Human brain from cases of epidemic encephalitis is infectious for both rabbits and monkeys, decidedly more so for rabbits. Only 20 per cent of monkeys are susceptible; on the other hand, at most 50 per cent of rabbits have a natural immunity. It has been possible, by repeated transmissions through rabbits, to obtain a fixed virus which is more potent for monkeys. It has been found likewise that with "fixing" of the virus a definite incubation period is established. Filtration, refiltration and glycerolation all tend to increase the incubation period. Material for inoculation was taken usually from the midbrain where the most pronounced lesions of this disease are found. Berkefeld filtrates of brain from 9 cases of epidemic encephalitis were injected intracranially with a total of forty-seven rabbits. Of these, twenty-four succumbed to the disease, the average incuba-

tion period being ten days. The virus was carried in series through as many as five generations. Encephalitis was produced in nine out of seventeen rabbits by means of emulsions of human brain from 3 cases, the average incubation period being five days. Here again the virus remained virulent through as many as five animal transmissions. Monkeys succumbed to inoculation of infected central nervous tissue in six instances. The clinical manifestations in many instances were remarkably like those found in the human. (See lethargic states, paralysis, convulsions and myoclonus.)

Dr. Harold T. Amoss and his confrères at the Rockefeller Institute, using similar material to that used by Loewe and Strauss, described above, have been unable up to the present time when the meeting was held (December, 1920) to verify the findings of the latter. For a description of their work the reader is referred to the chapter on laboratory experimentation.

CONFIRMATION OF FINDINGS OF LOEWE AND STRAUSS (WILLIAM M. THALHIMER). The epidemic encephalitis material on which my investigation and report are based consist of two spinal fluids and four autopsies. Mandler filters, tested to hold back bacillus prodigiosus, were used in preparing filtrates from the central nervous system. Rabbits were injected intracranially by the method of Loewe. Guinea-pigs were also injected by a similar method. Cultures were made on ascitic fluid tissue medium, as perfected by Noguchi. The brains of the rabbits and guinea-pigs which succumbed to the infection were removed with aseptic precautions. About 50 per cent of the rabbits succumbed after inoculation. They died on the average of from ten days to three or four weeks. Some of them apparently died rather suddenly and were found dead in their cages, after having been apparently well the day before. Various types of palsy appeared in some of the rabbits, corresponding to different types in human cases, such as peripheral palsy,

difficulty in swallowing, inability to swallow, typical myoclonus, etc. Palsy and apparent illness did not appear in guinea-pigs, the animals being found dead in their cages after having been apparently well.

The central nervous system of the rabbits and guinea-pigs showed typical lesions of epidemic (lethargic) encephalitis. These were not always the same and there was not always present the well-marked perivascular round cell infiltration. In some animals only minute hemorrhages were present. In the cultures of ascitic fluid tissue media a minute, filtrable organism, identical in all respects with that described by Loewe and Strauss, was cultivated from the original material and from material secured from the animals. Cultures of this organism were injected into rabbits and also into guinea-pigs and produced the disease with typical lesions. These animals did not die as quickly as those inoculated with the virus, as they usually lived from eight to twelve weeks after inoculation. The organism was again recovered from these animals.

This organism has been carried through many generations. Some of the strains are at present in the 12th generation.

Control cultural studies were made of the medium used and of all the types of the material cultured, with negative results. Control animals were inoculated with materials similar to the various types used in the experiments. These animals continued well. Some of them were sacrificed and showed no lesions in their central nervous system.

The results of this investigation are confirmation of both the experimental and the cultural studies of Loewe and Strauss.

The following questions submitted to Dr. Thalhimer before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask Dr. Thalhimer if his methods were essentially the same as were pursued at the Mt. Sinai Laboratory?

DR. THALHIMER: They were essentially the same. I think they were quite identical.

DR. SKOOG: Has Dr. Thalhimer had any training with Noguchi in the Rockefeller Institute prior to his work in this subject?

DR. THALHIMER: No. I had no training with Dr. Noguchi whatsoever. On several visits, however, to New York, I was with Dr. Loewe and Dr. Strauss at their laboratory, and they were kind enough to show me their work and their methods very thoroughly, and I was in communication with them quite constantly during the work, and can say that I learned a great deal from them as to how to conduct this work culturally and experimentally in animals, etc., and I also had the privilege and pleasure of having Dr. Loewe out in my laboratory for almost two weeks last summer, where I was able to show him my work and able also to give him some of my material which he brought back with him and I think also worked with.

DR. SACHS: May I ask whether the methods of the French authors, of Levaditi, etc., are identical with the methods that have been employed by these three gentlemen in this group?

DR. THALHIMER: There has been no publication by any of these other investigators as to the successful cultivation of a filtrable organism, and there has been no mention in the literature that I have seen that they have been using the tissue ascitic fluid culture method perfected by Noguchi. Whether that work is under way there or not one cannot judge from literature. So far as one can make out the nature of the filtrates which they have prepared,—and if I am wrong I hope you will correct me,—the nature of the filtrates that have been used, is very similar, and the injection of emulsions and things of that sort are of course simple methods and are necessarily identical. An important phase of the work is whether this is a filtrable virus and a filtrable organism; and there not having been published any work whatsoever on an organism it would leave that question unsolved. But the filtrates which they have used would confirm the work that has been done by Loewe and Strauss as far as the disease being caused by virus which will pass through a clay filter that will hold back ordinary organisms.

DR. LOEWE: They state definitely that virus experiments have been formed with definite filtrates, and in this case they use both Berkefeld's and Chamberland's filters. They make no mention at all of employing the Noguchi medium.

DR. SKOOG: Is every filtrable virus anaerobic?

DR. THALHIMER: I don't think that I can answer that. That would mean—Can one cultivate from a filtrable virus an organism only by anaerobic methods? Dr. Loewe seems to think he can answer that question.

DR. LOEWE: The cultural work done by Noguchi on his organism reveals the fact that after the organism has become saprophytized it is possible to grow the organism in the presence of oxygen, and Noguchi in his yellow fever work which also described the filtrable virus, filtrable organism, grows it in a medium and shows that certain strains will grow nearer the surface of the medium, indicating a necessity for a certain amount of oxygen being present.

DR. STRAUSS: Dr. Loewe has forgotten to state that we have attempted to grow this organism aerobically and we have failed. The question was: Is the virus necessarily anaerobic? A virus isn't anaerobic. A virus lives in any atmosphere. That is the answer. The organism that we have obtained from the virus is anaerobic, and until now we have not succeeded in growing it aerobically.

CONCLUSIONS OF THE COMMISSION

The Commission is of the opinion that final conclusions as to etiology, pathogenesis and incidence are not warranted at this stage of our knowledge of lethargic encephalitis. The general historical consideration of the disease, as discussed by Dr. Lewellys F. Barker, indicates the extent and the limits of our knowledge of lethargic encephalitis. The data furnished by Dr. Shirley W. Wynne indicate the extent, characteristics and mortality of the disease, not only in the neighborhood of New York, but in other localities; and the statistical material collected by Dr. Wechsler forms a particularly valuable contribution to the history of the disease in this country up to the time of his report. Comment is reserved on the observations of Drs. Leo Loewe and Israel Strauss and likewise upon Dr. William M. Thalheimer's report in Chapter VII.

It is well understood that at this stage of our knowledge the life history of the disease is not fully known. We know it

as yet chiefly in cross section. The characteristics of the causative organism are not fully established; the mode of conveyance cannot, therefore, be determined. Neither is the clinical course entirely appreciated in all respects. Further knowledge of the disease from all these standpoints is necessary before a final description and definition of it is warranted. It is one of those conditions, like syphilis, of which a life history is necessary before it is fully understood.

CHAPTER II

SYMPTOMATOLOGY: SYMPTOMS REFERABLE TO THE BRAIN

THIS chapter deals with the symptomatology of epidemic encephalitis referable to the brain. The general features of symptomatology are discussed by Dr. Lewellys F. Barker of Baltimore; the modes of invasion of the disease are discussed by Dr. Isador Abrahamson of New York City; the cerebral types by Dr. John W. McConnell of Philadelphia; the striatal and thalamic symptoms by Dr. J. Ramsay Hunt of New York; the auditory and vestibular disorders by Dr. Isidore Friesner of New York; symptoms referable to the eye by Dr. Ward A. Holden of New York; and cerebellar symptoms by Dr. J. P. Crozer Griffith of Philadelphia.

MODES OF ONSET (LEWELLYS F. BARKER). The initial symptoms of epidemic encephalitis have varied much in different epidemics. Thus, in the first Vienna epidemic, there was usually a fore-stage with symptoms of slight meningeal irritation, which was soon followed by somnolence and by ophthalmoplegia. In the 1918 epidemic in Australia, there was an initial stage of excitation (with headache and, sometimes, convulsions), and only several days later did the somnolence, the fever and the signs of paralysis appear. In the cases first observed by Netter in France (1918) symptoms of meningeal irritation were absent, but fever was more common than in the Viennese experience; the symptomatic triad described by Netter consisted of fever, somnolence and ophthalmoplegia externa. English observers (1918) recorded asthenia, malaise, headache, general pains, chills, nausea, anorexia and catarrhal inflammations of the respiratory tract as symptoms of the initial stage, to be followed in a

few days, or sometimes almost at once, with any one of several clinical pictures (somnolence with ophthalmoplegia; bulbar paralysis; catatonic stupor; or, comparatively frequently, a Parkinson-like syndrome). In the United States, initial stages of various sorts have been described. When the onset was sudden, there was often severe pain in the head, fever, and delirium, followed by a period of improvement for a few days, after which apathy, somnolence and cerebral nerve paralyses of different sorts or Parkinson-like syndromes developed. When the onset was more insidious, the initial symptoms often consisted of diplopia and slight mental confusion, or, in some cases, of neuralgias or of pareses in the domain of one or more of the cerebral nerves; and these patients, too, often showed improvement for a few days only to become somnolent later. Not infrequently there was marked restlessness at night with insomnia before a stage of somnolence was reached. In the Hamburg epidemic of 1918-19 described by Nonne, such an initial stage as above described does not seem to have been marked, the disease frequently having been ushered in by paralyses in the domain of the cerebral nerves or by a Parkinson-like syndrome. In the recent epidemic in Italy, Switzerland, Austria and parts of Bohemia (1919-1920) the prodromal phenomena have consisted of anorexia, headache, vague rheumatic pains, sometimes diplopia, and slight fever lasting for three or four days. Then somnolence and external ophthalmoplegia followed as in other epidemics, but in addition, certain hyperkinetic phenomena (myoclonia, choreatic disturbances of motility, etc.) have been very common. During 1920, hyperkinetic cases have been occurring also in America. It would seem probable, now, that some of the cases described in France as early as 1917 as "Cruchet's disease" were instances of the hyperkinetic form of epidemic encephalitis.

PRODROMATA AND INVASION (ISADOR ABRAHAMSON). Le-thargic encephalitis has the prodromata common to all

general infections. There are in addition certain special characteristics. Thus a catarrhal inflammation accompanied by fever of a certain degree and course, and by certain changes in the contents of the blood and cerebrospinal fluid, may raise the possibility of lethargic encephalitis; concomitant eye symptoms may increase that possibility to a probability; and the mental picture may make that probability a certainty. The nasopharyngeal area of the respiratory tract is the mucous membrane usually infected, but in one case or another, almost every mucous membrane in the body may be affected. The lining of the auditory passages seldom escapes; and the nasal and accessory sinuses are very often attacked too. Sometimes the bronchial mucosa, sometimes the intestinal is the main seat of invasion. And the localization or spread of the catarrhal inflammation may further serve to multiply differences between individual cases. But whether a rhinitis, or a sinusitis, or otitis, or an enteritis, or a pneumonia dominantly confronts us, the morbid process is fundamentally the same.

From the initial site of attack the toxin is diffused throughout the body, but the organisms tend to spread chiefly along the lymphatics of the nerve trunks. Hence, to local catarrhal inflammation and general toxemia, are added signs of implication of the nerve structures in anatomical connection with the first infected mucous sites. In the middle ear involvements, otic ganglion pain and seventh nerve weakness appear; in sinus involvement, the fifth nerve; in nasopharyngeal involvement, the medullary and upper spinal nuclei; in gastro-intestinal involvement the dorsolumbar cord. While, as a rule, the attack, having become evident, reaches its height and then progressively declines within a period of ten to twenty days, sometimes it lasts longer, and sometimes it is intermittent and sometimes it recurs. In such cases, we are dealing either with reinfections or with multiple infections or with a wavering resistance.

It is noteworthy that the main stress of this infection falls upon the most highly organized cells, the nerve cells.

The more highly organized a cell is, the more vulnerable it is. When all cells are exposed to the same toxic agent, the more vulnerable suffer most; and the rest suffer in the order of their vulnerability. And among the nerve cells certain cells are more delicate than others. Hence, the function of thought almost invariably is deranged in lethargic encephalitis. We see somnolent, maniacal, depressive and other psychotic cases. Again, we should emphasize the necessity of considering such cases not as types of disease but as types of reaction; not so much from the point of view of the organism as from the point of view of the individual. The functional derangement is excited by the infection, but the form and the degree of the derangement are determined, at least in part, by the circumstances which determined the mental constitution of the case. The infection evokes not a special type of the disease but makes manifest a latent weakness in the mental make-up, and this weakness may persist after all other evidence of the infection has passed away.

The following questions submitted to Dr. Abrahamson before the Commission, together with the answers to them, are here reported *verbatim*:

DR. DANA: Do you think it is well established and agreed upon by all observers that the disease always begins by attacking certain mucous membranes, so that these can be observed to be attacked and to be diseased?

DR. ABRAHAMSON: A careful study of the histories which has been neglected by the other observers—they have gone right to the lethargic encephalitis and neglected the original point—will elicit that practically every one has started with some catarrh of one of the mucous membranes. If you read the histories in literature, they mention this, but pass it by and regard it as a symptom of fever. I have seen it begin originally with conjunctivitis of one eye, followed by a fearful pain in the face, and then a neuromyolytic ophthalmia of that one eye.

DR. DANA: You have stated that the more highly organized the nerve cell the more vulnerable it is to attack. Do you not con-

sider the motor nuclei of the third nerve as more highly organized than those of the rolandic area?

DR. ABRAHAMSON: There are certain accidental conditions in the disease. In the first place, I am speaking of the general effects of the toxemia of lethargic encephalitis, causing the general symptoms, such as lethargy and changes in the mental states which occur at the same time. It is an accident, owing to the nasal localization, that the oculomotor nuclei are involved. That is an accident of the spread of the infection from the nose and throat to the pons, which I thought I brought out in the paper, but the general effect of the toxemia of the disease causes the nuclei to be lethargic, and causes typical mental symptoms which I believe are characteristic and present in every case.

DR. DANA: In other words, if you had the poison or toxemia of this disease and could inject it into a man or an animal, do you think it would affect his physical functions first and the more highly organized cells of the cortex, and would not affect the midbrain?

DR. ABRAHAMSON: I believe that if you inject the toxin intraperitoneally, the oculomotor nuclei would not be especially involved. This is not established; it is my opinion only.

DR. DANA: In the experiment on animals, does it work that way?

DR. ABRAHAMSON: The toxin has been injected intraperitoneally and the spinal cord has been involved along with a more general involvement, but it is difficult in animals to differentiate as to mental changes. All humans show mental changes.

DR. DANA: In describing or classifying this disease, would you not, after all—apart from any question of accident on account of the nasopharynx being near the midbrain—say that practically all of the disease groups itself around the midbrain syndrome? After all, you look for symptoms due to some trouble with the midbrain and motor nerves of the eye, and particularly the motor functions, as being the dominant thing right through.

DR. ABRAHAMSON: The dominant point of entrance after all happens to be the nasal pharynx. You have to postulate away the point of entrance, and I think it is definitely proven that the infection passes through the nerve sheaths. Those of you who are familiar with the work of Orr and Rows may remember that by

placing capsules of bacteria at various levels they got infections corresponding to the level at which they placed the capsule, and the nearer the point was to the capsule the more diseased it was, and the further away it spread from the capsule of germs the less the disease was. It is a fact that the majority of cases begin in the nasopharynx. There are spinal types, too. I have seen three definite spinal types.

DR. DANA: I would like to ask you if you get many symptoms involving the functions of the olfactory nerve?

DR. ABRAHAMSON: That is a very difficult thing to test in these individuals. In the first place, we have not laid much stress on it because so many have rhinitis and pharyngitis that it is very difficult to test the olfactory function. Again, during the lethargic stage, it is very difficult to test these individuals so far as the olfactory function is concerned. The olfactory function varies so much that one can hardly lay much stress on it.

DR. TAYLOR: From a practical standpoint would you overthrow all the classifications which you allude to in the beginning,—all the types? I am speaking purely from a practical standpoint.

DR. ABRAHAMSON: Dr. Wechsler who will speak upon types, has collected about 38 types, I believe. I think they create confusion, and especially when we regard the chronic cases. When you see the chronic cases and you see the mental cases and find that the make-up of the individual is responsible for most of the mental reactions in the mental cases, just as is the case in influenza,—that is the reason I accentuate the make-up of the individual and the type of resistance rather than the localization.

DR. TAYLOR: That is the theoretical. What I asked was whether we should stop at theorizations and not carry them out to the practical.

DR. ABRAHAMSON: No, I would not absolutely throw them over, but I think, rather than anatomically, I would go according to the severity of the disease in the way one does ordinarily in infectious diseases.

DR. TAYLOR: You say “the severity of the disease.” Would you call the paralysis agitans, type A, more severe than the psychotic type?

DR. ABRAHAMSON: No.

DR. TAYLOR: That is a vague idea, it seems to me.

DR. PATRICK: I would like to inquire whether you have any definite evidence that in this disease the virus travels from the nasopharynx along the nerve trunks to the midbrain?

DR. ABRAHAMSON: There is nothing definite. I am giving you a clinical view, not a pathological view.

CEREBRAL TYPES (JOHN W. McCONNELL). This term should be applied only to those cases that exhibit a symptomatology in consonance with the known anatomy and physiology of the cerebrum. This would include such symptoms as headache, vertigo, delirium; hebetude; euphoria; an unusual tendency to facetiousness; liability to automatism and to the automatic reproduction of familiar movements in purposeless fashion; speech disturbances and amnesias, the latter however most commonly seen in cases presenting marked hebetude; convulsions, both general and Jacksonian; monoplegias; hemiplegias with increased deep reflexes, Babinski's sign and persistent ankle clonus. Lethargy, somnolence and insomnia are symptoms mentioned in order of the frequency of their occurrence, the lethargy being less marked than the clinical signs pertaining to the motor system. Occasionally, the fulminating character of the symptoms suggested a cerebral apoplectic form of epidemic encephalitis.

In the cases observed there was little deviation from the symptomatology of recorded cases. The aphasia was of the so-called motor type. Perception was intact, but the ability to use articulate language was gone. The paralytic phenomena were associated with increased reflexes, Babinski's sign and persistent ankle clonus. Lethargy was noticeable and could probably be better termed apathy. Insomnia was found in one case in the height of the disease; in one or two others in the convalescent stage. The absence of sensory features, or rather the emphasis of motor features was a striking observation in all cases.

The accompanying clinical histories give a picture of the so-called *cerebral type*.

Case I. A man, aged sixty-two, clerk by occupation, was admitted to the University Hospital early in 1920, having been ill for about two weeks with headache, vomiting, fever, and general prostration associated with double vision. On admission he was somnolent, confused, disoriented, and showed some weakness of ocular muscles, together with slight weakness of the right face. There was no weakness of the extremities. The tendon reflexes were normal. During his stay in the hospital he gradually developed a right hemiplegia, with inability to speak distinctly. The tendon reflexes were increased on the right side; ankle clonus was obtained as well as the Babinski sign. He became addicted to facetious remarks, most of which were without foundation or relation to conversation. He was delusional, and expressed ideas of great wealth. The hemiplegic state lasted about one week and cleared up without any vestige remaining. His improvement was gradual but steady. During convalescence there was insomnia, headache, inability to concentrate, and weakness of the lower extremities. At the present time he is apparently well, all of his major and minor symptoms having disappeared.

Case II. A woman, aged seventy-one, suffered a mild attack of influenza in 1918, from which she wholly recovered. For four weeks previous to my seeing her she complained of general headache, feverishness, physical weakness and verbal amnesia. She was more somnolent than usual. In this lethargic state she presented the appearance of bilateral ptosis, but could elevate the upper lids by putting all her energy into the act. Gradually she lost strength and was forced to go to bed, having developed a complete inability to speak and a weakness of the right face, right arm and right leg. At this time she was apathetic, somnolent and was aroused with difficulty. Efforts to get answers to questions were fruitless because of her aphasia. She seemed unable to cerebration sufficiently to pantomime. She had no demonstrable disturbance of the cranial nerves. The eyegrounds were not pathological. She was not deaf and she could see. No disturbances in the fields of vision were demonstrable. She had a right-sided hemiparesis with increased reflexes, Babinski's sign and ankle clonus. The left side was not involved. She had no incontinence of urine or feces. There was no demonstrable sensory defect. There was no stiffness of the neck or of the spine, and Kernig's sign was absent, no tâche cérébrale. The diagnosis of epidemic encephalitis was made. She became

more stuporous, less responsive to external stimuli, and without any change in her motor condition died from exhaustion two weeks later. Necropsy was not allowed.

The following questions submitted to Dr. McConnell before the commission, together with the answers to them, are here reported *verbatim*.

DR. DANA: Is there not a better word than "cerebral" type to indicate the group of cases that you are referring to? What is a cerebral type from your point of view?

DR. McCONNELL: My point of view of the "cerebral" type is the same as yours; but I took it, the way the title was given to me, that I was to devote my attention to the portion of the brain exclusive of the basal ganglia and medulla oblongata, etc.

DR. DANA: I was wondering whether the term "pallidal" type would not be better than "cerebral."

DR. McCONNELL: I should think so.

DR. TAYLOR: The adjective "cerebral" belongs to the forebrain and the midbrain.

BASAL GANGLIA GROUP: STRIATAL AND THALAMIC TYPES (J. RAMSAY HUNT). Of clinical manifestations, those related to the corpora striata have aroused, perhaps, the greatest interest. This is partly due to the recent advances in our knowledge of the function of these structures, but also to the extreme rarity of this localization in other types of inflammatory disease. No other acute affection of the central nervous system has yielded so many, and such striking evidences of involvement of the great basal ganglia as encephalitis lethargica.

While the optic thalamus is frequently involved in encephalitis, the thalamic symptoms are milder and less serious than are those of the striatum, and the chief emphasis of this study will be placed upon the latter.

Anatomical Considerations. The corpus striatum is a large ganglionic structure which is divided by the anterior

limb of the internal capsule into two parts, the nucleus lenticularis and the nucleus caudatus. The nucleus lenticularis is still further subdivided into an external segment, the putamen, and an internal, which is termed the globus

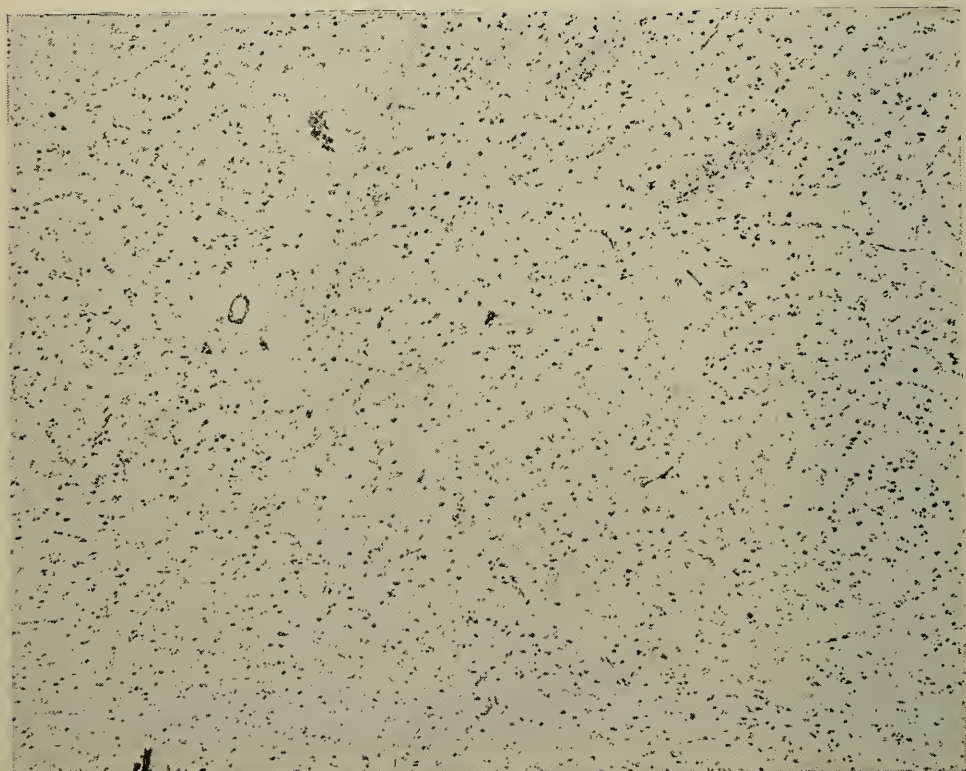


FIG. 2. Juvenile paralysis agitans of twenty-five years' duration. Section through the putamen. Note the increase of the glia nuclei and almost complete absence of the large pallidal cells. The small ganglion cells are not reduced in number.

pallidus. These anatomical divisions are based upon the gross appearance of the ganglion and are purely topographical.

The putamen and caudate nucleus are identical in histological structure and constitute the *neostriatum*.

The globus pallidus is composed of two segments, an inner and an outer. This portion of the striatum is older phylogenetically and is termed the *paleostriatum*.

A much greater importance is to be attached to the cellular types of this region than to the gross anatomical appearance and subdivisions.

The paleostriatum (pallidum) contains aggregations of



FIG. 3. Juvenile paralysis agitans. Section through the globus pallidus, showing atrophy and diminution in the number of the motor cells. Note the increase of glia nuclei and irregularly formed concretions.

large multipolar cells, which are histologically of the motor type (paleostriatal or pallidal cells).

The neostriatum (caudate and putamen) is composed of two cell types. Of these, the more numerous are small, polygonal cells which give the characteristic histological picture of this region (neostriatal cells). Scattered among these cells, are cells of much larger size. These are giant

multipolar cells, containing Nissl granules and deposits of yellow pigment, and are of the same type as the motor cells of the pallidum (giant pallidal cells of the neostriatum).

The motor or pallidal type of cells is present, therefore, in both paleostriatum and neostriatum; while the small neostriatal cells are peculiar to the neostriatum.

In 1917 I was able to demonstrate in juvenile paralysis agitans, widespread atrophy and loss of the large pallidal cells of the corpus striatum, and referred this disorder to a primary atrophy of this motor projection system of the corpus striatum (*primary atrophy of the pallidal system*). The peculiar and characteristic feature of this lesion was its limitation to a special system of motor neurons.

When the pallidal system is diseased there is produced the motor syndrome which we associate with paralysis agitans. This is characterized by paralysis of automatic associated movements, muscular rigidity and rhythmical tremor.

The writer also pointed out that the small ganglion cells of the neostriatum which were well preserved in juvenile paralysis agitans, showed extensive degeneration and atrophy in Huntington's chorea. The small neostriatal cells were, therefore, regarded as coordinating and inhibitory in function. Because of this elective atrophy of special systems of cells the syndrome chorea was referred to a loss of the *striopallidal* or *neostriatal system*, and the syndrome paralysis agitans was referred to a loss of the *pallidal* or *paleostriatal system*.

Two fundamental syndromes of the corpus striatum were therefore recognized, based upon the differences of function of these two cellular systems.

This conception of the function of the corpus striatum which the writer formulated in 1917, is not at variance with the other syndromes which have been ascribed to this region, but rather tends to reconcile and explain certain contradictory features.

The Vogt syndrome based upon a destructive lesion of the neostriatum, is characterized by choreic and athetoid movements, spastic diplegia (without pyramidal involvement) and dysarthria.

In this syndrome both cell types of the neostriatum, the small neostriatal cells and giant pallidal cells, are the seat of a destructive lesion, the clinical result of which is an admixture of the symptomatology referable to both systems. There is muscular weakness and rigidity associated with choreiform and athetoid movements. The choreo-athetosis is regarded as a choreiform manifestation to which has been added a certain degree of muscular rigidity, which would ensue from involvement of the motor cells of the neostriatum.

The Wilson syndrome, on the other hand, based on the progressive lenticular degeneration produces a more extensive lesion of the corpus striatum. Here the paleostriatum and the neostriatum are both involved, the symptoms of which are paralysis, muscular rigidity, and tremor of the paralysis agitans type associated with clonic and tonic spasms, and in some cases involuntary movements of a choreiform and athetoid nature.

Here again there are evidences of involvement of the two essential neuronal systems of the striatum. The paralysis, rigidity and tremor are dependent upon involvement of the pallidal system, while involuntary motor disturbances, namely, the clonic and tonic spasms, and choreo-athetoid movements would be occasioned by a destruction of the striopallidal system.

The great variation in the symptomatology of the corpus striatum is therefore dependent upon the relative degree of involvement of these two systems. When the neostriatum is chiefly affected, the choreo-athetoid element of the symptomatology is more in evidence; when the pallidal mechanism is chiefly involved the dominant symptoms are those of paralysis agitans.

Symptomatology. Encephalitis lethargica has given rise

to almost every possible variety and degree of involvement of these two fundamental systems of the striatum.

These manifestations have been slight or severe, tranistory or progressive, general or local. In addition many bizarre and fragmentary motor manifestations have been observed which were probably also of striatal origin.

This study is based on the analysis of 25 cases in which evidences of striatal involvement were present at some period of the disease.

Symptoms referable to the corpus striatum occur very frequently in the acute stage of the disease, and are evidently associated with an early localization of the inflammatory process in this region. They may also appear at a later period, after all acute symptoms of the disease have subsided. Very remarkable is the appearance of striatal symptoms as late sequelæ, weeks or even months after apparent recovery, suggesting a recrudescence of the infectious process.

Striatal symptoms are of two types corresponding to the two chief syndromes of the corpus striatum, as already defined.

There is a *pallidal type*, characterized by paralysis agitans; and there is a *neostriatal type*, characterized by choreiform movements.

While these two clinical syndromes may appear in pure form there is often an admixture of the two, as a result of which many curious clinical pictures are produced.

Mixed striatal types are characterized by a combination of the symptomatology of both paralysis agitans and chorea, a mixed paralysis agitans-choreiform type.

Of the two, the paralysis agitans type is the more frequent and usually the more severe in its manifestations. This is probably due to the course and relations of the pallidal system and the closer proximity of the paleostriatum to the midbrain which is the chief center of the inflammatory area. Of the 25 observations, 18 were of the paralysis agitans type, 4 of the choreiform type, and 3 were mixed striatal types.

Pallidal Type (Paralysis Agitans Type). The paralysis agitans type is characterized by fairly acute involvement of the voluntary musculature. Within a brief period of two or three days, there develops the typical muscular rigidity, postural deformities, mask-like expression of the face and the paralytic disturbances of motility characteristic of paralysis agitans.



FIG. 4. Corpus striatum; presenile paralysis agitans. Note diminution of the fiber network of the globus pallidus. The internal capsule is well preserved.

Generally speaking the tremor is much less constant and when present less conspicuous than in true paralysis agitans. This is probably caused by the sudden development of massive rigidity which masks the tremor, producing the clinical type known as *paralysis agitans, sine tremore*.

When tremor is demonstrable at this stage it is usually slight and localized in the tongue, face or hands. The characteristic pill rolling movement which we associate with paralysis agitans is quite rare and I have only observed it as a

late residual symptom in 2 cases, and never in the acute stage.

One side is frequently more affected than the other, and *hemilateral types* are encountered in a late stage of the disease. Even more limited forms occur (*segmental types*), as, for example, isolated involvement of the face (the Parkinsonian mask). Involvement may also be limited to the upper or lower extremities. Segmental types I have only observed after the subsidence of the acute stage, as a late residual manifestation.

The tremor may show a similar limitation and typical rhythmical tremor may be hemilateral or sometimes segmental, i. e., confined to the head, an arm or a leg. These fragmentary clinical types are usually encountered only as late or residual symptoms.

The rhythmical tremor when present is often coarse and increased by movement. It is then an action tremor, and is increased, not diminished, during the passage of a movement. In this respect it differs from the classical tremor of paralysis agitans, but is very similar to what has been observed in the earlier stages of the juvenile paralysis agitans (primary atrophy of the pallidal system).

True paralysis agitans is produced by a progressive lesion of the *pallidal system*, which is atrophic or degenerative in nature, while the paralysis agitans of encephalitic origin is merely a symptomatic manifestation due to injury of the pallidal system by inflammatory lesions or toxins. As the acute lesions subside, the clinical symptoms disappear, which explains the often rapid improvement in this group of cases. We are not accustomed to this favorable outcome in true paralysis agitans, which is a progressive disorder. Recoveries are, however, noted after inflammatory lesions affecting other motor systems, and it is only interesting to note that the pallidal system is no exception in this respect.

A *cataleptic type* of encephalitis has also been described. The association of general muscular rigidity of the paralysis

agitans type with the peculiar lethargy characteristic of epidemic encephalitis produces a clinical picture closely resembling catalepsy (*flexibilitas cerea*).

Abortive Type. It is also interesting to note that in the acute stage of the disease mild transitory striatal symptoms are sometimes present. These consist of a certain tightness or tenseness of the musculature, a certain monotony and mild

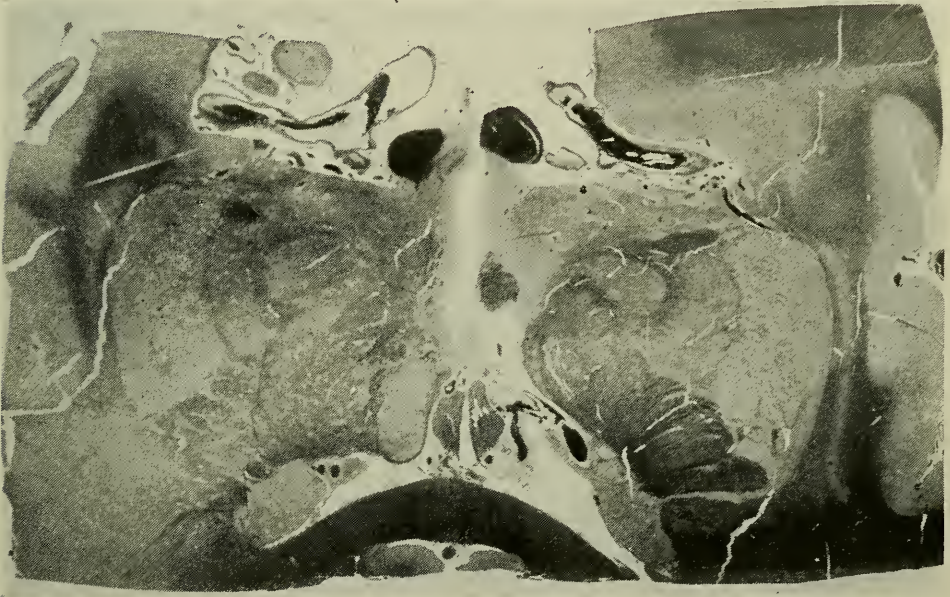


FIG. 5. Presenile paralysis agitans. Vertical section through middle of corpus striatum, showing thinning of the ansa lenticularis.

fixity of expression, with slight tremors of the tongue, face or extremities which disappear as the acute symptoms subside.

Progressive Type. A tendency to progression in the paralysis agitans group is not uncommon. In my experience this tendency has been greater in those cases in which the symptoms make their appearance late in the disease, or as relapses after improvement or apparent recovery. It would appear to depend upon a renewal of the inflammatory process, or an actual lighting up of old lesions.

A *relapsing form*, unfortunately not uncommon, is a well-

recognized type of the disease. Its existence has been emphasized by von Economo, Buzzard and Greenfield.

Pallido-Pyramidal Types of Encephalitis. In previous studies of the symptomatology of the efferent pallidal system of the corpus striatum by Ramsay Hunt, attention was directed to the existence of *pallido-pyramidal types* of palsy. This form is characterized by a combination of the symptoms of both spastic paralysis (pyramidal tract system) and paralysis agitans (pallidal system), and is by no means uncommon because of the close anatomical relationship of the internal capsule and the corpus striatum.

In pallido-pyramidal types, the paralysis is more complete because both the pyramidal and extrapyramidal systems are involved; the one controlling isolated synergic movements of cortical origin, and the other striatal movements of the automatic associated type. The muscular hypertonicity is also greater and combines the peculiar features of spasticity and paralysis agitans rigidity. Especially characteristic of the pallido-pyramidal type are exaggerated tendon reflexes, clonus and the Babinski phenomena of the spastic type in conjunction with a loss of automatic associated movements of the striatal type. It is rather remarkable that, in this series of 25 cases of striatal encephalitis, definite involvement of the pyramidal tracts was noted in only 3 cases.

This is all the more peculiar as we are dealing with a rather diffuse disseminated inflammatory reaction, a type of lesion which one would naturally expect to involve the adjacent pyramidal system of the internal capsule and pes pedunculi. It is possible that certain toxins of encephalitis may possess a special affinity for the cellular systems of the striatum, which render it particularly susceptible to the infection.

The Neostriatal Type (Choreiform Type). The other essential syndrome of the corpus striatum which may develop as a result of epidemic encephalitis is chorea. The choreiform movements of striatal origin are involuntary and irregular in character and are of the automatic associated type. According to the view which has already been expressed, they

represent a motor discharge of the striatal mechanism in contrast to paralysis agitans, which is a paralytic manifestation.

The choreic movements may be general, hemilateral or segmental (local) in their distribution. They may vary somewhat in character, e. g., mild and severe, large and small amplitude, and occasionally rhythmical. A certain degree of hypertonicity is sometimes present, giving an athetoid character to the movement. Athetosis, or choreo-athetosis, I would regard as an admixture of chorea and muscular rigidity due to involvement of both the neostriatal and pallidal systems.

Acute Choreiform Type. Some writers on the subject of encephalitis have described cases characterized by generalized choreiform movements appearing in the acute stage of the disease, associated with delirium and other severe psychotic symptoms. A clinical picture very similar to the *chorea insaniens* of systematic writers. Archambault has reported cases of this type, as have also Oehmig in Munich and Dimitz in Vienna.

Choreo-Athetoid Types of Movements. In addition to chorea, movements of an athetoid and choreo-athetoid type may also occur, both in the early and late stages of the disease; of special interest is their appearance as late sequelæ, months after apparent recovery. The movements of this type, like those of chorea, may be general, unilateral or segmental (local) in distribution. They differ from chorea in being slower, more stereotyped, and associated with hypertonicity of the affected muscles.

In the more localized forms there is a peculiar repetition of slow stereotyped movements occurring at regular intervals. These, except for the limited and rather fragmentary character of the movement, are very similar in their character to other well-known forms of choreo-athetoid movements of striatal origin.

Belonging to this group are other types of movement of somewhat larger amplitude which affect more particularly

the trunk and root portions of the extremities, causing curious contortions of attitude and gait. Some of these movements bear a striking resemblance to those observed in the dystonia group of motor disorders, which, since the autopsy report of Thomalla (*dystonia lenticularis*) must now be definitely allied with the symptomatology of the striatal body.

Rhythmical Chorea (Bradykinetic Oscillation). This disorder of motility varies somewhat from the recognized lenticular types. It is characterized by slow rhythmical movements of an extremity, sometimes involving both the arm and leg on the same side, and occurring with great regularity, 18 to 20 movements to the minute. With the slow rhythmical oscillation of the extremity there is a simultaneous hardening of many of the muscles of the arm or leg, showing the diffuse nature and wide distribution of the muscular contractions. This form of spontaneous movement, in my opinion, is referable to the extrapyramidal system and in all likelihood to the striatal mechanism. It differs however in the monotonous regularity of its synchronous rhythm and stereotyped repetition from other forms of striatal movement.

Marie and Levy have described cases of this character as *bradykinetic oscillation*, and emphasize the peculiar nature of this type of movement and its lack of correspondence with any recognized clinical type. While agreeing with these writers as to the unique character of this curious spasmodic type, of which 4 cases occurred in my series, there is a strong resemblance to certain types of movement which I have occasionally observed in the dystonia musculorum deformans. I would, therefore, regard it as related to the neostriatum.

Acute Chorea of Childhood (Chorea of Sydenham). Before leaving the neostriatal type, it will be interesting to mention some recent work on the chorea of Sydenham. Attention has already been directed to the fact that certain well-recognized types of epidemic encephalitis were observed in sporadic form, long before the existence of the present

epidemic. The question naturally arises, Have other clinical types of infection of the central nervous system a similar origin and relationship?

A recent pathological study by Marie and Tretiakoff of the nervous system from a case of chorea is very suggestive from this point of view. The case was a typical one of Sydenham's chorea, occurring in a child, aged ten, and which terminated fatally ten days after the onset of the disease. Evidences of inflammatory reaction were found throughout the brain and spinal cord, with the exception of the bulb and cerebellum. The neostriatum and central cortex were particularly affected. These investigators, having also studied the lesions of epidemic encephalitis, emphasize their great resemblance to those found in the central nervous system of Sydenham's choreas. Their observations would suggest a possible relationship between the acute infectious chorea of childhood and the choreic type of encephalitis lethargica. The occurrence of neostriatal symptoms in such a case, with evidences of diffuse involvement of the nervous system, I would explain by a special affinity of the toxin for the neostriatal system of neurons (striopallidal system).

Mixed Striatal Type (Mixed Choreiform and Paralysis Agitans Types). While the paralysis agitans and choreiform types may occur in pure form, it is well to emphasize the fact that these two clinical pictures are not infrequently combined in greater or lesser degree. Indeed, among the most striking features of involvement are the many bizarre combinations which combine both the elements of chorea and paralysis agitans.

Rare Myoclonic Types. Occasionally one observes, after an attack of encephalitis, rhythmical movements of the distal portion of the extremities. In one of these cases which presented typical symptoms of paralysis agitans, there was rhythmical flexion of all the fingers, occurring about 20 times a minute. Movements of this type are so fragmentary that it is rather difficult to localize them with certainty.

The association with paralysis agitans and the stereotyped regularity of the movement are in favor of a striatal origin.

Rhythmic twitchings of the face and jaw, either alone or in combination, have also been observed. When combined, the movements of the jaw and face may be synchronous. Such manifestations may represent disjointed fragments of striatal motility or may indicate a release of kinetic impulses in subsidiary centers of the pons varolii which contain the motor nuclei governing the facial muscles and mastication.

Bilateral Synchronous Myoclonia. There is still another type of movement which has been encountered in this disorder, the classification of which is somewhat difficult in the present state of our knowledge. This is a movement of the myoclonic type, involving a large number of muscles and causing bilateral synchronous movements of the trunk and root segments of the extremities occurring in very rapid tempo—50 to 60 to the minute.

These movements differ from those of the “myoclonus multiplex type of spinal origin” in the large number of muscles which are simultaneously involved, and the extent of the locomotor effect. They are also unlike those types of movements which we associate with the striatum.

Hamill has described a group of cases representative of this type, in all of which the movements were increased during sleep in contrast to the ameliorating effects of sleep on the pure striatal types. He suggests their relationship to certain subordinate motor centers in the pons or medulla, which in conjunction with there spiratory center act as auxiliary centers of breathing.

I have also observed movements of this type. In my opinion they are neither cortical nor spinal, and if they do not represent lower forms of movement under striatal control they are probably referable to some infrastriatal mechanism of the paleokinetic system of motility.

Thalamic Types. The *optic thalamus* is the sensory counterpart of the corpus striatum. It is the great ganglion station

where the neurons of the sensory paths terminate for their final grouping and distribution.

Some of these neurons terminate in the optic thalamus itself, subserving the *affective sensibility*; the great number pass to the sensory area of the cerebral cortex to subserve the higher form of discriminative sensibility.

Lesions in this region may produce sensory symptoms of the following character: Spontaneous pain of intolerable intensity and of persistent character; loss of superficial and deep sensibility with anesthesia; ataxia and astereognosis. There may also be present slight hemiplegia, as well as choreic and athetoid movements. The sensory loss and pain are alone of thalamic origin, the other symptoms are referable to surrounding parts.

Symptoms of thalamic origin are not infrequent in cases of epidemic encephalitis. They are often associated with evidences of striatal involvement, but in my experience are neither so severe nor well defined. I have observed no case presenting the complete thalamic syndrome as outlined by Déjérine and Roussy. My experience has been limited to sensory symptoms which it seemed reasonable to assume were of thalamic origin, although one could not deny their possible relationship to the central sensory mechanism of the spinal cord and brain stem.

The most frequent symptom of thalamic involvement in encephalitis, in my experience, has been pain. This may be of agonizing intensity and is very resistant to all analgesic remedies. It may be generalized or localized and may persist for weeks or months. It is difficult to differentiate localized thalamic pains from those referable to the posterior gray matter and posterior root system of the spinal cord. In differentiation, I would lay some stress on the coexistence of striatal symptoms which would appear to show inflammatory involvement of both structures at the same level. In no case have I encountered any extensive anesthesia, either superficial or deep. Tactile sensation has shown little or no involvement, and the chief sensory disturbances when

present have been of pain and temperature sensibility. In no case was the deep sensibility affected.

From my personal experience, and that of others, I am inclined to believe that the thalamic symptomatology is largely limited to intractable and persistent pain associated with mild evidences of sensory loss, especially of pain and temperature sensibility.

As the optic thalamus is the sensory counterpart of the corpus striatum and as both ganglia are closely connected by short commissural systems, it is interesting to speculate on the possible rôle which irritative lesions of the thalamus may play in the production of striatal types of movements, such as chorea and athetosis. While the facts of pathological anatomy point to the neostriatum, and especially the neostriatal system as the seat of the essential lesion of chorea, it cannot be denied that an irritative focus in the pallidum or the thalamus might give rise to spontaneous striatal motor manifestations of the same character as those resulting from loss of its inhibitory mechanism.

The following questions submitted to Dr. Hunt before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TAYLOR: Do you make any distinction between the two parts of the corpus striatum in your localization of these or other lesions?

DR. HUNT: I do. The globus pallidus is the paleostriatum, and the caudate nucleus and the putamen represent the neostriatum of comparative morphologists. The small cell, *neostriatal system*, is related to chorea; the large motor cells, *pallidal system*, which I associate with paralysis agitans are found in the paleostriatum, but they are also present in giant cell form in the neostriatum. Hence I conceive the corpus striatum in terms of cellular systems rather than in terms of its larger anatomical constituents. This explains many of the curious phenomena in the symptomatology of this epidemic and of other striatal syndromes with which we are familiar.

DR. TAYLOR: Would you regard a late paralysis agitans type as a degeneration of the striata?

DR. HUNT: No; I would regard it as related to a recrudescence of the inflammatory process rather than to a slow degeneration. When paralysis agitans develops after all acute symptoms have subsided, or after an interval or period of apparent temporary recovery, I would associate this with an inflammatory process—a recrudescence, a lighting up rather than a slow degeneration, for the reason that if it were a degenerative process evidences of paralysis agitans would have been present at once in the acute stage.

DR. TAYLOR: Is there any evidence yet as to what becomes of the paralysis agitans types? So far as I have seen them they have steadily improved, but I have seen one case which after a year seems to me definitely fixed in a sort of paralysis agitans condition in part only. He has the mask-like face of paralysis agitans, but he has not got any of the tremors or rigidities. It looks like a case of paralysis agitans.

DR. HUNT: I think the consensus of opinion is that this group of cases tends to improve, tends even to get well. I have had 2 cases in which after a year there has been rather a tendency to progression and to relapses. Von Economo has reported the pathological histology of such a case in which there was this progression, with intervals of improvement and intermissions of both paralysis agitans and choreo-athetoid symptoms. He found post mortem both old and recent lesions, which I think proves beyond any doubt that in some forms of the infection the old lesions may come to a standstill while the infective agent is still active in the production of newer inflammatory lesions.

DR. TAYLOR: There are some cases that suggest the segmental arrangement of the automatic mechanism of the brain, but there are not any cases of the paralysis agitans type that show anything like a segmentation, I mean paralysis agitans showing only in the head or arms or in the legs. Have you seen anything that suggests a segmental arrangement?

DR. HUNT: Yes, I have referred to this in my paper as local or fragmentary types. I have seen cases in which the only symptom of paralysis agitans that I could detect was a very definite mask; another case in which there was a paralysis of the “paralysis agitans” or pallidal type of the lower extremities, not affecting

the arms, and I have also seen "paralysis agitans tremor" of the head with the mask, but with no other symptoms of the disease that I could detect.

DR. TILNEY: Does the age of the patient have any relation to the Parkinsonian type or choreic type?

DR. HUNT: I couldn't answer that very definitely except to say that I have seen the paralysis agitans type, or what I thought was the paralysis agitans type, at the age of two; and of course in the present epidemic it has not been uncommon in young people from eleven to fifteen. In this respect it is interesting to mention that ten years ago there was described a case of paralysis agitans resulting from encephalitis in the Bristol Infirmary. Frequent mention has been made in this meeting of the sporadic occurrence of various clinical types in previous years. It is interesting to know that this is true of the paralysis agitans type.

DR. ABRAHAMSON: Why use the term "paralysis agitans" to cover all the movements not choreiform?

DR. HUNT: I use the terms "Parkinsonian" or "paralysis agitans" because they are so fixed in the description of this particular group of symptoms. I have suggested and prefer the term *pallidal* to denote this fundamental type of striatal palsy. This term denotes the relation of the palsy to the pallidal system of the corpus striatum and is analogous to the use of the term pyramidal type of palsy, when the pyramidal tract or system is involved. When both motor systems, namely, that of the corpus striatum and internal capsule are simultaneously involved, as so frequently occurs in vascular lesions in this region, this I would term a pallido-pyramidal type of palsy.

DR. PATRICK: Do you think that all the abnormal movements arising from lesions of the striatal region can be classified either under the paralysis agitans or the choreiform types?

DR. HUNT: I do. The existence of an admixture of these two types or syndromes must however be recognized, namely, symptoms of paralysis agitans associated with those of chorea in various combinations and degree.

A MEMBER: I want to bring out whether in the various autopsies made in this particular encephalitis, anyone has investigated them to see whether the small cells are affected in the choreiform type and the other cells in the Parkinsonian type of disease—whether it is actually demonstrated or by analogy with what we already know.

DR. HUNT: No; this selective involvement has not been demonstrated in encephalitis, but only in certain types of paralysis agitans and in Huntington's chorea. For example, in a case of acute chorea of childhood (Sydenham's chorea) reported by Marie, he finds lesions in their essential character similar to those of epidemic encephalitis. Those lesions were not limited by any means to the corpus striatum. They were present in but not confined to the neostriatum, and yet the essential symptom is chorea. This would suggest that the particular form of infection which produces the acute chorea of childhood has a selective action on the small inhibitory cells of the neostriatum and that this action is toxic in its nature; and while there are small scattered foci of inflammatory reaction throughout the central nervous system the chief effect of the toxin by virtue of this selectivity is concentrated on the neostriatum. This special selective action of the toxin on certain limited groups of cells or neurons is manifested in other clinical types of epidemic encephalitis, e. g., the myoclonic type.

CLINICAL ASPECTS OF NON-PURULENT INFECTIONS OF THE CEREBELLUM (J. P. CROZER GRIFFITH). Undoubtedly the epidemic of lethargic encephalitis has exhibited cases in which the process had affected especially the cerebellum and adjacent parts of the brain more than the cerebrum; but the vastness of the literature on the subject of this disease prevented any collection of cases of this sort.

The author had had under his care 4 cases of encephalitis in which the cerebellum had suffered very decidedly from the attack; indeed, in most of them bearing the brunt of it. There was great variety in the symptoms; but, basing the description of what might be called a typical case upon those observed by him, and upon the reports obtained from medical literature, it might be said that the principal acute symptoms consisted of unconsciousness and absence of speech, with later a very decided ataxia of the limbs, and often of the head and trunk, at first usually interfering entirely with walking or even with standing. Unconsciousness was reported in more than half of the cases. Although this was usually of brief duration, it sometimes lasted for weeks, and at times a soporose condition without entire unconsciousness

persisted for a much longer time. In some instances, instead of the soporose state, there was violent screaming, a state of fear, a maniacal condition, and a diminution of intelligence. Even apart from unconsciousness the mentality was affected in about two-thirds of the reported instances. In the cases improving most rapidly this disturbance of mentality might last but little more than a week. In others it sometimes continued for months, or even to some degree for years. Disturbance of speech was nearly always present; and by this was meant a disturbance apart from the loss of speech due to unconsciousness. With improvement of the general condition the speech returned, but was often drawling, slow, jerky, or affected in some other way. In a few instances, speech was entirely absent for months. Even in the milder cases the return of perfect control of speech was sometimes quite slow, the disturbance still being present in some instances over three years after the attack. Ataxia was observed in all the cases, and was usually an early and prominent manifestation. Sometimes the gait was typically drunken. The arms were involved also in most instances. Generally, the power to walk was regained in a few weeks, although the gait was far from perfect. The other symptoms which have been reported are oftener absent than present, and cannot be called entirely characteristic, although suggestive. Among them may be mentioned nystagmus and vertigo. The former is sometimes very marked.

The immediate causes of the disease have been varied. Some infectious disorder directly preceded the attack in about two-thirds of the cases. In one instance, trauma was reported as an immediate precursor; in another, dysentery.

The nature of the disease is of great interest. It is apparently without doubt an encephalitis, and also one which is not limited to any one portion of the brain. Symptoms other than those supposedly cerebellar have been seen in practically every case. Fever, unconsciousness, delirium, convulsions, and the like, indicate the involvement of some portion of the brain other than the cerebellum. The absence

of speech as the case progresses is due, apparently, to a lack of control, but early in the attack it probably depends upon unconsciousness or some other disordered mental state. It would appear to be clear that the cases upon which this report is based cannot be said to have been due to any specific micro-organism. The fact that but one case came to autopsy, and this many years after the attack, prevented any actual determination of the lesions which were present during the acute condition. The prognosis in general is good, at least so far as life is concerned; but the ultimate condition of the patient is uncertain. Some cases are on record which show that final complete recovery may take place, even though the symptoms have lasted for several years. A total duration of three or four months may be taken as an average for the more acute symptoms. Although it is probable that from one-third to one-half of the cases may be said to have recovered completely, a number of instances in the list indicated that there is decided danger of some symptoms remaining permanently, and among these is especially to be noted a persistence of some degree of mental defect.

The following questions submitted to Dr. Griffith before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TAYLOR: Would you regard the symptoms in these cases as predominantly cerebellar?

DR. GRIFFITH: I would, decidedly.

DR. TAYLOR: So that you may in justice assume that there were actual lesions of the cerebellum in these cases?

DR. GRIFFITH: I think so.

DR. WEISENBURG: What is the nature of the speech disturbances?

DR. GRIFFITH: It was irregular or jerky or slow, sometimes just an irregular speech. As it improved it became more regular but still slow; the child had to wait a bit before it could enunciate.

DR. WEISENBURG: In what way would the cases differ from the other types of encephalitis with which you have come in contact?

DR. GRIFFITH: You mean not cerebellar? They differed in their

irregular speech and particularly in the ataxia. There were no other positive symptoms; there were suggestive symptoms.

DR. WEISENBURG: In other words, you made the diagnosis on the obstructed speech and the ataxic movements of the arms and legs in the case?

DR. GRIFFITH: Yes.

DR. SACHS: May I ask Dr. Griffith whether he has seen in children distinct cerebellar cases beginning in very acute fashion and during the time of the epidemic, or whether he knows about such cases in which the cerebellar symptoms have been as definite as they could possibly be? I am referring especially to such cases in which the child in a very acute fashion shows no other symptom except an absolute inability to stand or walk. I remember one case, for instance, where the child had to walk around by the wall instead of crossing the room. I want to know whether any such cases have come to your attention without any cerebral symptoms?

DR. GRIFFITH: One of my cases began with ataxia—tumbled down the stairs—came on all of a sudden, and according to the parents' report there was no history whatever of any cerebral involvement of any kind that we could find with the exception of her ataxia, and that disappeared completely. She came to my office at my request a year or two later and everything seemed to be gone. That was, however, not the epidemic type. The only one I have seen in connection with the epidemic had distinctly cerebral symptoms as well, more marked than the cerebellar.

DR. BARKER: Were Dr. Griffith's cases coincident with influenza outbreaks or poliomyelitis outbreaks? And if he saw one of those cases today, could he differentiate it from epidemic encephalitis or would he take it to be encephalitis?

DR. GRIFFITH: I could not differentiate it because I think it is only a matter of position. I think the lesion would produce much the same symptoms.

AUDITORY AND VESTIBULAR LESIONS (ISIDORE FRIESNER). The following clinical studies are based upon 6 cases of epidemic encephalitis in which the manifestations were wholly, or in large part, due to disturbances of the auditory or vestibular apparatus. Four of these cases were observed by me in the past two and a half years. For the histories of the 2 remaining cases I am indebted to my colleagues. It

must be apparent, at a glance, that general conclusions regarding this phase of the disease cannot be well drawn from so meager clinical material, and yet the almost total absence of similar studies in the literature is, in itself, sufficient justification for this survey.

After a fairly thorough search of the literature regarding this disease I have been impressed with the comparative rarity of involvement of the eighth nerve. I have been able to examine the records of 145 cases of epidemic encephalitis treated at Mt. Sinai Hospital during the last two years. Among these there was one instance of bilateral total deafness. In many the stupor and the consequent lack of cooperation made complete functional ear tests impossible. However, with the exception cited above, there was no other evidence of eighth nerve involvement.

Barker, in his report of 8 cases, mentioned tinnitus as a symptom but once. Here the ears and presumably both the auditory and vestibular apparatus were normal. Eagleton reports a similar case with tinnitus and normal hearing. In Tilney's 20 cases there is no mention of auditory or vestibular manifestations. In Skversky's 10 cases the ears were normal. In Hall's analysis of 16 cases there is one with vertigo and tinnitus. Functional tests are not recorded, but the general manifestations of the disease were far more severe than those of any of the cases observed by me. Occasionally, one meets with recorded evidences of a disturbance in the vestibular apparatus, as in Alexander's Case II, where a vertical nystagmus upwards was present. Case IV of the series here reported showed a similar phenomenon due undoubtedly to a lesion in the pons. Mills and Wilson also report a case with vertical nystagmus upwards. Alexander and Allen reviewed 182 cases in the literature, and selected 100 from that number as being typical. In their analysis of the symptomatology of these cases there is no mention made of eighth nerve involvement.

Most of the cases in this series lacked some of the cardinal symptoms of epidemic encephalitis. Thus, in only one

instance was there either lethargy or asthenia. Cases of the type reported here, several of them with exceedingly circumscribed lesions, probably represent a very mild, or even an abortive form of the disease. Yet it has seemed that in all the cases the diagnosis was well established. An explanation of some of the cases on a basis of toxicity has been offered. One case was originally reported as an instance of botulism. Hall, however, has pointed out that the Cinderella foot of botulism will not fit into the glass slipper of this syndrome, and in the light of our later knowledge it must be considered a case of epidemic encephalitis with typical multiple lesions. Toxic agents may cause an endemic, rarely an epidemic; never a pandemic.

Case I. School-boy, aged nine. On April 30, 1920, he complained of tinnitus in the left ear, followed by vertigo, vomiting, and difficulty in walking. His temperature was never over 100°F. On May 3rd, examination showed no tympanic disease on either side. Normal hearing right; total deafness left. There was slight spontaneous nystagmus to the right and a positive Romberg. The direction of the falling was toward the left, but could be influenced by changing the position of the head. In the interval between May 3rd and May 10th, the date of the second examination, a lumbar puncture was done. The fluid was clear, containing no cells, and no excess globulin. On May 10th, falling was no longer regularly toward the left and could not be influenced by changing the position of the head. The total deafness persisted. The left static labyrinth, however, was normally irritable calorically, and there was normal vertigo and normal past pointing following stimulation. On May 19th, with a noise apparatus in the right ear, patient heard 26 double vibrations but not 2048 (C^d). On June 5th, with a noise apparatus, he heard a forced whisper: heard 26, and June 26th he heard ordinary conversation. The upper and lower tone limits are normal. The Weber is referred to the head. At this time he showed a peculiarity which has persisted to date, i. e., with a noise apparatus in his right ear, when one whistles with the lips, he interprets the sound as a grunt. Asked to imitate the sound, he reproduces the pitch of the tone accurately, but has no idea of its quality.

Remarks. This is an instance of total loss of function of the auditory branch of the eighth nerve with what was perhaps, in the beginning, a collateral edema of the vestibular branch. The slight, if any, loss of function in the vestibular branch disappeared rapidly. Some hearing returned in about three weeks from the onset of the disturbance. It is now, however, about seven months since the beginning of the attack, and it appears that we are justified in concluding that a total restitution of hearing in the left ear will not occur.

Case II. A jeweler, aged forty-two; never had any previous ear trouble. Was seized suddenly four days ago with tinnitus and deafness in the right ear. Slight pain, no vertigo. There was no tympanic disease. Weber was referred to the left. Rinne, left side plus, right side minus ad infinitum. The hearing in the left ear for voice, whisper, watch, etc. was normal. The tone limits were normal. The right ear was totally deaf. There was no spontaneous nystagmus, no falling, no past pointing. Rotation to the right and to the left was followed by a nystagmus of good amplitude lasting twenty-five seconds. Vertigo and past pointing were normal. Caloric of both right and left labyrinth positive in forty-five seconds. Both the vertical and horizontal canals were active on both sides. Blood and spinal fluid Wassermann, negative. Spinal fluid was under moderate pressure, clear, no cells, plus 1 globulin. After the lumbar puncture there appeared a weakness of the right facial of the central type, and right Babinski and Oppenheim. All these symptoms disappeared rapidly, and in July it was reported that the man had normal hearing.

Case III. That there are degrees of disturbances without total loss of function is illustrated by Case III. S. G., married; family and personal history have no bearing on present illness. Patient was in good health up to four days ago. At that time he had an attack of diplopia. A few days later there was some paresis of the facial muscles on the left side. He was tired and drowsy. Spinal fluid was obtained under normal pressure. Cell count was normal, and no excess of globulin was detected. Hearing on the right side was diminished to about one-half of what was present on the left side. The Rinne was positive, and he localized the Weber to the left ear.

Remarks. Taylor also reports a case with a bilateral disturbance of hearing of the nerve type.

Tinnitus is a symptom occasionally met with in lethargic encephalitis. Eagleton, however, has shown that tinnitus may occur in such a case with no demonstrable disturbance in hearing. Grahe, in his studies of the internal ear in lethargic encephalitis, states that in 6 of the 13 cases examined, the bone conduction was shortened. It is especially noteworthy that a case with shortening of bone conduction, but otherwise with normal findings, presented a perfectly normal duration of hearing by air conduction. Grahe is under the impression that there is no relationship between this condition and meningeal changes, since shortened bone conduction occurred both in cases with normal cerebrospinal fluid, and in others with pathological changes in the spinal fluid.

Case IV. A dentist, aged thirty-six, was seized with vertigo, nausea, vomiting, deafness in left ear, diplopia and ataxia which confined him to his bed for one week. He had no fever. He was unable to leave his home or to attend to his professional duties for several weeks, so that by the time he was seen during the fourth week of his illness, many of his earlier symptoms had disappeared. The history, in addition to the above, was that his blood Wassermann was negative. His cerebrospinal fluid showed no cells, globulin content normal, Wassermann negative. The otological tests were as follows. Weber is referred to the head. Rinne, both sides positive. Schwabach, slightly shortened both sides. The upper and lower tone limits are normal for both ears. Tested with a noise apparatus, both ears hear low conversation readily. With the exception of the slightly shortened Schwabach, the hearing of both ears is normal. *Static Labyrinth.* Station is good, very little swaying. There is no spontaneous past pointing in the right arm; the left arm past points 2 inches to the left. This persists on repeated tests. There is a spontaneous nystagmus of the rotary type directed to both sides, slightly more marked to the right. There is also a vertical nystagmus upward. Rotation to the right is followed by a horizontal nystagmus of fair amplitude, lasting twelve seconds. Rotation to the left is followed by a nystagmus of very good amplitude, lasting twenty-five seconds. *Tests for Vertigo.*

Rotation to the right; the right arm touches, the left arm past points 1 inch to the left (spontaneous past pointing). Rotation to the left; both arms past point 2 inches to the left. Caloric reaction of right vertical canals positive but faint, one minute and fifteen seconds. No past pointing in either arm. Stimulation causes diplopia. Caloric reaction of the right external (horizontal) slightly more marked than that of the vertical canals. No past pointing in either arm. Caloric stimulation of the right external canal arouses an oblique nystagmus upwards. Caloric reaction of left vertical canals positive faint, fifty-seven seconds, reaction of external canal more marked. No past pointing in either arm.

Remarks. The hearing is normal. There is a spontaneous nystagmus to both sides and also upward. Functional tests show an interference with all reactions following stimulation of the left labyrinth. Caloric stimulation of the right vertical canals causes diplopia, of the right external canal an oblique nystagmus upwards. The nystagmus following stimulation of the right labyrinth is nearly normal while the vertigo is markedly suppressed. These facts indicate that the lesions are not peripheral, but are situated in the brain stem and probably in the cerebellum as well.

Case V. F. W., physician. Was seized about March 4, 1920, with an attack of vertigo, nausea and vomiting. On March 5th and 6th there was diplopia. The vertigo continued for three days and gradually subsided within a week. Never any fever or headache. At the end of the week he was examined. There was no tympanic disease. The hearing of both ears was normal. There was a coarse rotary nystagmus to the left. In walking he swayed to the right, and supported himself in his right side. Unfortunately no other stimulation was applied to the static labyrinth, except rotation. This was repeated several times, and showed definitely a total loss of reaction, i. e., of both nystagmus and vertigo on rotating to the left, whereas on rotating to the right there was a normal nystagmus lasting twenty-two seconds, with normal vertigo.

Remarks. There may be some question as to the validity of the conclusion that we are dealing here, so far as the ears are concerned, with an isolated lesion of one vestibular

nerve. It may be remembered, however, that this patient fell to the right, that he supported himself on his right side, that he had a typical rotary vertigo, with objects moving about to his left and that he had a spontaneous rotatory nystagmus to the left. These facts, with the results of the rotation tests, seem sufficient to warrant our conclusion.

In conclusion, it may be stated that lesions of the eighth nerve in epidemic encephalitis are rare. This rarity may be more apparent than real, for Eagleton, in his examination of 4 cases, states that he was able to demonstrate disturbances in the vestibular apparatus in every one of the four.

The involvement may result in a diminution of, or a total ablation of function. I have had no personal experience with lesions affecting both branches of the eighth nerve followed by total ablation of function, but Mills and Wilson report 2 such cases.

Either the auditory or vestibular branch may be involved.

Judging from the number of cases examined and reported, there is an unusual proportion of vestibular lesions. The virus appears to exercise an exceedingly fine selective action.

Restitutio ad integrum occurs perhaps more frequently in the vestibularis than it does in the cochlearis.

The polioencephalitic cases, with exceedingly limited lesions, undoubtedly represent an abortive type of the disease in which many of the cardinal symptoms of epidemic encephalitis are lacking.

The diagnosis in the absence of other confirmatory findings is based upon the exclusion of middle ear disease, of tumor, the absence of the usual serological findings, and other evidences of syphilis, and finally upon the occurrence of these cases during an epidemic of encephalitis followed by fairly rapid recovery.

The following questions submitted to Dr. Friesner before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: Evidently Dr. Friesner himself has found some things entirely peculiar to this disease?

DR. FRIESNER: Yes; this one instance, which I studied in connection with Dr. Strauss, I have been unable to explain satisfactorily to myself. It is an exceedingly curious phenomenon; I do not know what it means. This child is able to reproduce accurately the tone of my whistle, but is unable to grasp the quality of the tone. In other words, asked to reproduce the pitch he sings the note accurately, but when I ask him, "What noise did I make?" he says: "You grunted." I do not think my whistle is anything like a grunt. He reproduces the pitch but not the quality. He is an exceedingly intelligent chap, about ten years old.

DR. DANA: When he reproduced your whistle did he whistle or grunt?

DR. FRIESNER: He grunts. I have him close his eyes, and I put the noise apparatus in the ear with which he hears normally, and I whistle. Then I ask him what sound he heard and he grunts. I ask him to sing the note and he produces the pitch accurately, and he does that whether my whistle is high-pitched or low-pitched. I never have seen that before nor has any other otologist with whom I have spoken, but it is really present and there cannot be any question about it, because I have tested him at least four or five times since he first showed this curious thing.

DR. DANA: You make a diagnosis of encephalitis in these cases largely by exclusion, do you not?

DR. FRIESNER: Frankly, most of the diagnoses are made by the attending neurologist or physician; it is only because of the ear symptoms that I have been asked to examine cases.

DR. DANA: Nevertheless, you concluded by giving the data for making a diagnosis practically by exclusion.

DR. FRIESNER: I did that. Of course, as I have said, these data are so meager that it is almost impossible to draw any conclusions. With regard to the diagnosis, that statement was passed upon one case; this case was referred to me because he had tinnitus and deafness. When I examined him I noted that he had none of the usual phenomena which occur with specific disease, and at once it occurred to me that it might be an instance of lethargic encephalitis. A subsequent examination of the man and the development of facial paralysis proved that my supposition was correct.

DR. SACHS: You are willing to believe that just as there are

some cases of lethargic encephalitis where there are chiefly eye symptoms, it may be that some exhibit chiefly ear symptoms?

DR. FRIESNER: Yes. There is one thing I would like to ask. I have stated in my conclusions and have called these cases "polio-encephalitic" cases. I wonder whether it is not more correct to call them "polyneuritic." When I looked to see in what category I could place these cases, I examined the divisions in your book and I found that they fitted only into what you called the "polio-encephalitic cases," but it seems to me these are nerve lesions, not nuclear lesions, and I wonder whether "polyneuritis" is not correct or "mononeuritis."

DR. TIMME: May it be central?

DR. FRIESNER: I do not know. There have been very few cases reported of total deafness of central origin. I never have heard of them in anything like an inflammatory state such as one gets with encephalitis.

DR. DANA: You mean you do not get total deafness in one ear from a central lesion?

DR. FRIESNER: There are a few cases reported with tumor on one side and an abscess on the other, or tumor on one side and hemorrhage on the other, in both lobes.

DR. DANA: I mean a nuclear disease of the cochlear nerve. Is that not called deafness in that ear?

DR. FRIESNER: I am not aware of any such case. I do not think we can differentiate between a nuclear disease, causing true deafness, and a nerve disease that is a true neuritis.

DR. STRAUSS: What other disease could cause these symptoms if not encephalitis?

DR. FRIESNER: The subsequent development of this one case, of which I speak, and which came to me with total deafness, could not be caused by anything else than encephalitis, but, this opinion may be due to my faulty observation when he came to me. All I was able to determine was that he was totally deaf in one ear, and that it had occurred but four days previous to my examination. That is all he had—total deafness. The static labyrinths on both sides were perfectly normal. The first case, and I am depending on your word, was lethargic encephalitis.

DR. SACHS: Could any other disease have caused it, or do you know of any other disease?

DR. FRIESNER: Not as regards the first case.

OCULAR MANIFESTATIONS (WARD A. HOLDEN). The eye symptoms noted in one hundred consecutive case histories of epidemic encephalitis at Mt. Sinai Hospital are as follows:

A. *Opticus Symptoms*. Blurring of the optic discs in 4, papilledema in 1.

B. *Oculomotorius and Abducens Symptoms*.

1. *Ptosis*. Of both eyes in 45, of one eye alone in 11—56 patients in all.

2. *Extrinsic muscles of the eyeball*.

Paresis or paralysis of both external recti in 17; of the right external rectus alone in 14; of the left external rectus alone in 13—44 patients in all.

Paresis or paralysis of both superior recti in 1, of both internal recti in 4, of the right internal rectus alone in 1.

Paresis of both internal and both external recti in 2.

Paralysis of all muscles supplied by one 3d nerve in 1.

Paralysis of conjugate dextroversion of both eyes in 2.

In all, weakness of the oculomotor muscles that would give rise to diplopia in 56 patients.

Nystagmus in 32 patients.

3. *Pupils*. Irregularity in 15, inequality in 20. Sluggishness or absence of light reflex in 35 patients, in 13 of whom the convergence or accommodation reflex was sluggish also.

The irregularity and inequality of the pupils in 28 of the 35 cases were in eyes with sluggish pupils, so that irregularity and inequality not associated with sluggishness were noted but 7 times.

4. *Accommodation*. Weakness of accommodation in both eyes in 1.

C. *Facialis Symptoms*. Weakness of some or all of the muscles supplied by the facialis of both sides in 24, of one side in 49—73 patients in all.

The most marked divergence from these percentages is in the carefully studied 8 cases of Barker, Cross and Irwin

(*Amer. J. M. Sc.*, cliv., 2-3). They found partial ptosis in 3, sluggish pupils in the entire 8, and weakness of accommodation in 4. Their reports on the recti muscles are less specific.

The percentages in the thirty histories reported in Tilney and Howe's book "Epidemic Encephalitis," are similar to the Mt. Sinai Hospital percentages except as regards the recti muscles. Tilney and Howe found the *internal* rectus paretic more frequently than the *external*.

Opticus Symptoms. There was noted in 4 patients at Mt. Sinai Hospital a blurring of the optic discs and in one a definite papilledema.

The earlier reports on encephalitis referred in many cases to blurring of the discs. But we recognize that a slight edema and a reddening of the discs due to dilatation of the capillaries, with overfilled and perhaps tortuous retinal veins, is a fairly common condition when the general circulation is sluggish. In such cases a subsequent examination is made and if the condition remains unchanged we do not regard it as a beginning papilledema and we are strengthened in this belief when the patient complains not of headache and vomiting, but merely of cold feet. It is possible that some of the cases of blurred optic discs reported may have had but little significance.

True papilledema was noted in 1 Mt. Sinai Hospital patient and was found in 1 of the 20 at the Neurological Institute. The latter patient, a child three years of age, had meningeal symptoms, paresis of both external recti, paresis of the right facialis and right hemiparesis, with papilledema of two and a half dioptries elevation in each eye. She made a complete recovery. In another case with papilledema, verbally related, there was found at the autopsy an extensive subcortical hemorrhage in the parietal region which had caused hemiplegia.

True papilledema then is a very rare symptom of encephalitis and seems to occur only where there are unusual complications. This papilledema is doubtless the result of

increased intracranial pressure in most cases, although in some cases it may be due directly to meningitis.¹

OCULOMOTORIUS AND ABDUCENS SYMPTOMS. Inflammatory changes have been found widespread in the brain, but with great frequency in the brain stem, consisting of edema, hemorrhage, proliferation of neuroglia, circumvascular exudation of leucocyte-like cells, and degeneration of ganglion cells. The meninges also are frequently inflamed. From this it is evident that there may be pressure upon the nuclei of the ocular nerves, upon the supranuclear and infranuclear fibers—direct and association—and upon the trunks of the nerves at the base of the brain. This pressure may be transitory or permanent, slight or destructive, or even alternating and recurrent. It is obvious that clinically one must find in this disease all degrees of muscular palsy and all possible combinations and varieties of palsy of the third and sixth nerves, with changes from week to week.

¹ C. P. Symonds in a paper on "Optic Neuritis in Encephalitis Lethargica," *Lancet*, Dec. 18, 1920, after describing four cases studied at the Johns Hopkins Hospital, gives as one of his conclusions the following statement: "In the association of optic neuritis with acute disseminated myelitis we have an instance of involvement of the optic nerves in a diffuse inflammatory process affecting the nervous system, which is analogous to the association of optic neuritis with encephalitis lethargica."

In *Archives of Ophthalmology*, vol. xl, No. 6, and vol. xliii, No. 3, I described five cases of optic-nerve affection in acute disseminated myelitis. In this disease the affection of the optic nerve is a localized inflammation about certain blood-vessels in the nerve. There is, as a rule, no elevation of the disc and there ensues a partial or general pallor of the disc, with marked disturbance of vision. In 3 of the 4 cases in which visual tests could be carried out I found a lateral hemianopic defect in the field of one eye only, which seemed to me characteristic of the disease, and in one case an excessive concentric contraction of the field of one eye.

The reports of optic-nerve disturbances in epidemic encephalitis lethargica with which I am familiar, including those of Symonds, show little in common with the optic-nerve disturbances I have seen in acute disseminated myelitis. Therefore, until anatomical proof to the contrary is presented, I prefer to regard the optic-nerve disturbances of epidemic encephalitis as being chiefly of the papilledematous type due to increased intracranial pressure, rather than of the retrobulbar inflammatory type, as Symonds would seem to suggest.

In general, in this disease, we find a disinclination to use the eye muscles or a quick fatigue and return to the position of rest after using them, even when there is no well marked paresis. In this, as in many disturbed mental conditions, the patient may dislike to look up and may simulate paralysis of upward movement unless repeated tests are made.

Ptosis. In the lethargic state the patient may lie with his eyes closed in the position of rest and often cannot be urged to keep them open, or even to open them wide for a moment. This may be due to a mental disinclination, to photophobia, to a dread of diplopia, or to a spasm of the orbicularis palpebrarum muscles, as well as to weakness of the levators. When he can be urged to open his eyes a difference in the width of the palpebral apertures may be seen or a drooping of one or both upper lids may be noted, but except in the unusual cases of complete third nerve paralysis, complete ptosis is not likely to be present. In other cases the eyes are kept open, but winking is infrequent. Forcible closing of the eyes often leads to a marked tremor of the lids, for tremor is a very constant symptom of encephalitis. When one eye has been kept closed a few days to prevent diplopia, its palpebral aperture will be narrower than that of the other eye when both are opened. One can easily realize that the question of ptosis in a given case may admit of a variety of answers. Ptosis was noted in fifty-six of the Mt. Sinai Hospital patients.

Extrinsic Muscles of the Eyeball. Certain brain affections have rather definite paralyses of the ocular muscles which are pathognomonic. Thus after diphtheria there may be paralysis of accommodation on both sides without pupillary disturbances; in botulism there may be ophthalmoplegia interna on both sides—that is, iridoplegia and dilatation of the pupil with paralysis of accommodation; in polioencephalitis superior the two internal recti are first paralyzed and later often one or both external recti; in destruction of one abducens nucleus there is conjugate paralysis of dextro- or sinistro-version of the two eyes; in red nucleus involvement there is loss of upward movement of the eye; and with

exudation at the base of the brain both sixth nerves or both third nerves in some or all of their branches may be affected.

In epidemic encephalitis almost all of these paralyses are found. And if there is anything at all characteristic it is the *frequent association of ptosis with paralysis of the external recti*. In the Mt. Sinai Hospital group there were twenty-three patients in whom paralysis of one or both external recti (without accompanying paralysis of internal recti) was associated with ptosis of one side or both. This is a combination of third and sixth nerve affections that is rarely met with in any other disease.

The fourth nerve doubtless is affected at times in encephalitis, although paresis of the superior oblique muscle has not been noted in any reports recalled. This may be because a paresis of the superior oblique might easily be overlooked in a lethargic patient, and even in a mentally alert patient it might escape notice when masked by more obvious palsies of other motor muscles.

There is a curious condition, of whose pathology we are ignorant, known as paralysis of divergence. In this condition there is neither paralysis nor spasm of the recti muscles and the mobility of each eye is normal, but the eyes are converged on a point some 15 cm. away and see single at this distance, while at greater distances there is homonymous diplopia in every direction of the gaze. The etiology of this condition is obscure and the lesion is supposed to lie in a purely hypothetical divergence center. It has been seen in midbrain tumor and in uremia. This paralysis of divergence was one of the earliest symptoms in a patient with encephalitis, and two colleagues have said that they had found the same condition in encephalitis patients, so probably it is not very rare if carefully sought for; and study of the cases in which it is present may lead to our better understanding of the condition.¹

¹ In some cases, paralysis of divergence has either preceded or followed paralysis of one external rectus, suggesting that the site of the lesion in this condition lies near the abducens nucleus.

It would be natural to assume that there is a break in the association

The course of these palsies is not uniform; often they disappear in a few days, sometimes they are permanent, sometimes they are recurrent. In general we may say that diplopia disappears early, ptosis later, and pupillary anomalies and weakness of accommodation last of all the eye symptoms, many months after the onset.

Nystagmus. There may be the slight nystagmus of asthenic states or the pronounced nystagmus of organic brain disease. Very frequently too there are the nystagmoid twitchings in the direction of action of a muscle that is parietic. One variety of irritative spasm that has been described to me is a lightning-like oscillation of the two eyes, without parallelism of action, coming on at intervals when the eyes are in the position of rest. These different varieties have not been differentiated in our figures, but nystagmus was noted in 32 of the Mt. Sinai patients.

Pupils. In 35 of the 100 patients there was defective light reaction of the pupils, often with irregularity and inequality. As a rule in encephalitis the sluggish pupils are small or of medium size. They differ from the pupils of cerebral lues only in the greater frequency of an accompanying defective convergence reaction. The characteristic pupils of cerebral lues are seen also at times with tumors and non-luetic inflammations in the brain stem. In encephalitis this symptom is very common, Barker finding it in every one of his reported cases.

tract between the abducens nucleus of one eye and the nucleus for the internal rectus of the other eye. However, we believe that the impulse which turns both eyes to the right arises from the right abducens nucleus. And if this impulse were sent from the abducens nucleus in normal measure to the right external rectus and incompletely to the left internal rectus the result would be divergence of the two eyes and not the convergence which is found in these cases. Could we assume that the impulse which turns the eyes to the right arises from the nucleus of the left internal rectus, an interruption of the association fibers in the longitudinal fascicle would prevent the full impulse from reaching the right external rectus and thus lead to convergence of the eyes. But since this assumption seems untenable, our attempts to solve the problem with our present data are purely speculative and vain.

This is not the place to discuss the mechanism and manner of production of the Argyll-Robertson pupil, but it is hoped that study by neuropathologists of these brains with inflammatory changes still fresh may solve some of the unsettled problems.

In lues, if there is a paresis of accommodation there is also dilatation of the pupil and iridoplegia—an ophthalmoplegia interna. A peculiarity of encephalitis pupils is that in many cases there is a paresis or even complete paralysis of accommodation without dilatation of the pupil—in other words there is a normal pupil or an undilated Argyll-Robertson pupil plus the paresis of accommodation that formerly we saw as an isolated symptom in diphtheria alone. This paresis of accommodation in encephalitis, furthermore, is usually bilateral, whereas in lues it is mostly found in one eye only.

The characteristic features of the sluggish pupil found in encephalitis then are, first, the great *frequency of accompanying defective convergence reaction*, and second, *the association often with paresis of accommodation without dilatation of the pupil*.

Accommodation. Accommodation may be apparently normal by the tests, yet the patient may not be able to maintain it for a length of time, that is, there is quick fatigue of accommodation, or there may be various degrees of actual loss of accommodation. When there is actual loss of accommodation the hyperopic patient, who is accustomed to overcome his hyperopia by exercising his accommodation, finds that his distant vision has suffered as well as his near vision. And the emmetropic patient finds that he can read print only with great effort and by holding it at arm's length. This paresis of accommodation may easily be overlooked in the bed patient, but the ophthalmologist finds it frequently in the convalescent.

Facial Symptoms. The facial palsy is for the most part slight and often limited to the lower branches. It is rarely sufficiently pronounced to give rise to lagophthalmos or even to cause difficulty in closing the eyelids.

Since the eye disturbances of encephalitis are sometimes of early onset and then the most annoying of the patient's symptoms, the ophthalmologist may be the first physician to be consulted and in times of epidemic he may from the eye symptoms alone, if lues can be excluded, make the diagnosis.

The following questions submitted to Dr. Holden before the commission, together with answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask Dr. Holden whether he attaches any importance at all to the irregularity of pupillary contour that has been observed in these cases. You make a distinction; I believe you stated that the contour is irregular but with a sluggish pupil, just as though you associated those two things in some way, or are they in any sense independent?

DR. HOLDEN: I think we all feel that the pupil of cerebral lues, for example, begins with irregularity and inequality and is followed by a sluggishness of light reaction. These pupils seem to me to follow fairly well the model of the Argyll-Robertson pupil in its incipency. The irregularity in equality was noted in but 7 cases in which there were no sluggish pupils, nor sluggishness of light reaction.

!DR. DANA: Was there any case of sympathetic paralysis?

DR. HOLDEN: I have not found any notes of these. There is a record of one of the Philadelphia neurologists who reported a case of what he termed bilateral sympathetic paralysis. In other words, he had the slight narrowing of the palpebral aperture and the contracted pupil which we have as symptoms of the disturbance of the cervical sympathetic, and he regarded this as being unique in this disease as occurring on both sides; as a rule it is not observed. Now, as an ophthalmologist I would rather question the accuracy of his observation. I was not at all sure that his diagnosis was correct.

DR. SACHS: I think we have all seen some of those cases that should probably have gone in the first instance to the oculist. Tell us something about the length of time which you know that the ocular palsies have persisted in these cases. Have they been chronic?

DR. HOLDEN: Many of the cases that I saw in my office, of patients who came with the eye symptoms first, were afterwards sent to hospitals and were lost to my observation. I cannot answer that question definitely.

DR. BARKER: Dr. Holden has not said much about the fourth nerve. Was it involved in these cases, or does it usually escape?

DR. HOLDEN: There was no note of the fourth nerve involvement in the Mt. Sinai Hospital cases. I have not observed it myself. Naturally, in bed patients, the fourth nerve involvements are difficult to make out. I have no doubt it has been involved in a good many cases, but this does not appear in the statistics.

DR. HALL: Could the small pupil be due to a sympathetic paralysis? Small pupils are quite common in encephalitis. Do you think it is an irritation of the oculomotor? Why is there miosis?

DR. HOLDEN: My theory about all these pupils, the luetic pupil and the others, is that there is an irritation to begin with which causes an irregular contraction of the sphincter muscle. First we have an irregularity and later a small pupil. I cannot see any reason for dragging the sympathetic into these cases.

DR. HALL: Dr. House of Oregon has spoken especially of weak movements of both eyeballs—inability to do much of anything with any of the eye muscles—what might be called a sluggish eyeball as contrasted with sluggish pupils. What would Dr. Holden's idea be of the lesion that could cause such a phenomenon as that—sluggish eyeball, where all the movements are paralytic.

DR. HOLDEN: I think it is rather difficult to say except that I regard a certain number of those cases as purely mental such as we have all noticed in examining patients in the hospital; for instance, that it is very difficult to get almost any of those patients to look upward, and in these encephalitis patients it is very difficult to get them to look aside sometimes. I have to give tests to be sure that the patient has not paralysis. Of course, in the cerebellopontile angle tumors we find what we may term a disinclination. The patient requires a good deal of urging to turn his eyes to the right in the case of right tumor. It is difficult, I think, to distinguish between the cases of mental disinclination and those in which there is actual nerve weakness.

DR. DANA: Referring to the sympathetic again, did not Dr. Cadwalader report other symptoms which belong to cervical sympathetic paralysis, like sweating and reaction of the pupils, etc.?

DR. HOLDEN: As I remember it, the report was about thirty lines long only, and I do not remember that he mentioned other symptoms.

DR. PATRICK: You spoke in rather a cursory way of the possibility of various varieties of the spasm of the ocular muscles as well as the paralysis. Might I ask if you have seen ocular spasms in these cases and to what extent?

DR. HOLDEN: After I had written this paper I crossed out "spasm" and then I put it in again, because there were some cases reported of the spasm of the orbicularis. I think some of these cases might come under the head of "spasm." I have not seen any other.

DR. SACHS: Have you seen what we have described as cogwheel movements of the eyeballs? Have you been struck by the jerky movement of the eyeball? We thought that the expression "cog-wheel" movement would about express it.

DR. HOLDEN: I think I have.

CONCLUSIONS OF THE COMMISSION

Mode of Invasion. Members of the Commission are of the opinion that no dogmatic statement can be made at the present time as to the exact mode of invasion of the infective agent.

The suggestion, therefore, that the mucous membranes are the seat of primary involvement, the infection then extending along the lymph paths must be accepted with reserve; also the statement that nerve palsies are related to the primary and original site of infection.

While the importance of the lymphatic system in the extension of inflammatory affections of the central and peripheral nervous systems is now well recognized, the blood-stream is no less important.

In any investigation of this question, therefore, the hematogenous, as well as the lymphogenous, factors should receive consideration.

The statement was also made that the more highly organized cells of the central nervous system are more subject to the ravages of the disease.

The Commission is of the opinion that while the general principle may be recognized, that the higher the degree of organization of the nerve cell the greater its vulnerability, this does not apply to infections of the type under consideration. Here other factors must be considered and especially one which is rather obscure at the present time, namely, the elective affinity of certain bacteria or their toxins for certain groups of nerve cells.

Special Clinical Type. It has been the custom in the classification of all general infections of the central nervous system to designate special clinical types in relation to anatomical structures, e. g., cerebral, cerebellar, spinal, etc.

Strict anatomical divisions in general infections of the nervous system are always arbitrary and the type is rarely so definite as its name would indicate and is often only indicative of a predominant symptomatology.

This appears to be true of the so-called cerebral and cerebellar types of encephalitis. These types are not only rare, but where they do occur they are associated with other focal symptoms which blur the purity of the clinical picture.

In some cases the cerebellar symptomatology is to be ascribed to lesions involving the cerebellar connections in the midbrain rather than to the cerebellum itself.

Basal Ganglia Group. One of the striking clinical features of this disease has been the involvement of the corpus striatum with the development of symptoms of paralysis agitans and of chorea as pure clinical types or in combination. The relationship of chorea, choreo-athetosis, dystonia, and paralysis agitans to the corpus striatum has been shown by a number of studies in recent years. Their occurrence in connection with the predominantly brain stem involvement of epidemic encephalitis is therefore not surprising, although practically unknown in other types of infection of the central nervous systems, as, for example, epidemic poliomyelitis. Of special interest is the occurrence of symptoms of both paralysis agitans and chorea, practically in pure form, which would appear to favor Ramsay

Hunt's conception of the two striatal systems,—the one motor, for the control of automatic and associated movements (pallidal system); and the other exercising an inhibitory and coordinating function (neostriatal system).

It is to be hoped that careful studies in the future, including serial sections of this region, will throw additional light on these important questions.

CHAPTER III

SYMPTOMATOLOGY: SYMPTOMS REFERABLE TO THE SPINAL CORD AND PERIPHERAL NERVES

THIS portion of the section on symptomatology of epidemic encephalitis concerns the coincidence of this disease in parts of the central nervous system other than the encephalon, and the Commission submits clinical and laboratory observations as follows: The report of Dr. Henry A. Riley of New York, upon spinal types of the disease, and the report of Dr. Foster Kennedy of New York, upon peripheral and radicular types. Also, the report on laboratory findings, of Dr. Walter M. Kraus of New York, and of Dr. Irving H. Pardee of New York, gives the serology of the spinal fluid and blood in epidemic encephalitis.

SPINAL TYPES OF EPIDEMIC ENCEPHALITIS (HENRY A. RILEY). This form was late of recognition being considered first as an aberrant form of poliomyelitis associated with somnolence. Only the increasing number of cases made it evident that there was a distinct form of spinal involvement of epidemic encephalitis.

Pure examples of any one form or type being almost unknown, only the predominating picture determines the label to be applied to the disease.

Figures by Wechsler show that out of 864 cases, 44 cases were described as myoclonic, 29 as radicular, neuritic or neurologic, 24 as meningitic, and 1 as dorsal poliomyelitic, a total of 121 cases. On account of the loose description and terminology, only 23 cases can be considered as spinal, these being myelitic, paraplegic and ventral poliomyelitic.

The forms of epidemic encephalitis which are apparently mainly spinal in character may be divided into two groups:

1. The ventral poliomyelitic form.
2. The transverse myelitic form.

The ventral poliomyelitic form may be divided into two sub-groups:

- a. The irritative type.
- b. The paralytic type.

Rarely seen as clear-cut entities, these merge one into another; the paralytic type is often the end result of the irritative. The irritative type may clear up without any permanent defect; the paralytic may develop full blown.

Irritative Type. The literature is not clear in definite distinguishing features in motor disturbances, observations being mixed and conflicting. The character of movement is the criterion by which the level of the disturbance may be identified.

a. The cortical level is distinguished by the movement being a purposeful synergized movement, presenting elements which distinguish not only the cortical pattern and concept, but also the collaboration of the cerebellum in the movement; for example, the movement displayed in Jacksonian epilepsy. The arrangement of the Betz cells and the ventral horn cells makes the cortical type of movement a synergized movement, and not an aimless contraction of independent muscles or muscle fibers. Such cortical stimuli are incapable of bringing about myoclonic or fibrillary contractions.

b. The striate level is distinguished by the movements which we know as the choreas, the athetoses and the mobile spasms. The underlying feature being the automatic associated type of movement, we can differentiate these from the spinal level of motility.

c. The cerebellar level need not be considered, for we do not have any definite type of abnormal involuntary movement from stimulation of the cerebellum.

d. The spinal level of movement characterizes the myoclonic and the fibrillary manifestations of epidemic encephalitis. Such contractions at most produce a movement of a single muscle, and at their least produce a movement of a single muscle fasciculus. They are simple purposeless irregular movements. The coarse myoclonic movements are twitching, exceedingly rapid in rate, irregular in rhythm and variable in extent. At times slow vermicular movements have been observed, probably due to the stimulation of connector neurons in the spinal gray and the resulting correlated activity of several neuron groups. The myoclonic form was often preceded for several days by radicular pains and the interval may indicate the time necessary for the infective agent to spread from the roots to the parenchyma of the cord itself.

Paralytic Type. The paralytic type of the ventral poliomyelitis form, closely resembles that seen in poliomyelitis; in fact, of itself it is indistinguishable from that disease. The history and concomitant phenomena establish the differential diagnosis.

The transverse myelitic form of epidemic encephalitis is similar to the transverse myelitis seen in other forms of spinal disease and varies with the site and extent of the lesion. By some it has been considered not as a definite type but as an accidental occurrence in the course of a typical spinal encephalitis, the result of hemorrhage or thrombosis. Occasional xanthochromia may substantiate this view.

CASE REPORTS

Case I. An irritative type from the service of Dr. Foster Kennedy at the Neurological Institute, New York City.

Onset seven weeks before admission, with pain and soreness spreading from the head to the entire body; retention of urine, transient diplopia, insomnia and tremor.

Fixity of facial expression; coarse tremor of upper and lower extremities, transient cogwheel in flexing forearm, brief jerky

movements of the toes and feet and myoclonic contractions of dorsal muscle groups in the thigh. Abdominal myoclonus. Deep reflexes sluggish, abdominals absent, no pathological reflexes. No sensory changes of note. Slight external rectus weakness on the right side. Laboratory examinations negative.

Case II. A myoclonic fibrillary type.

Onset with pins and needles sensation, then pain in left instep, which was sharp, localized and stabbing. This spread to right leg, and then subsided and was followed by twitching movements in calves, thighs and abdomen. Patient delirious, hallucinating with expansive tendencies for some time.

Could not walk on heels or toes. Gait was steppage. Cerebellar function normal. Left knee-jerk strong; right knee jerk weak. Ankle reflexes absent. Abdominal reflexes present on right and doubtful on left. No pathological reflexes. Muscle strength diminished in abductors of thighs both sides. Adductors of thighs, left, affected more than right. Extension and flexion of feet very weak. Atrophy of left thigh and calf. Sensory: Some change over right L₅—S₅; left L₂—S₅. Right pupil larger than left with normal reactions.

Case III. A transverse myelitic form from the service of Drs. Frederick Tilney and Hubert S. Howe at the Presbyterian Hospital, New York City.

Onset with dizziness, diplopia, headache, left facial paralysis. Right ptosis.

Reflexes of upper extremity, active; of lower extremity, absent; no abdominal or pathological reflexes. No movement of lower extremity except slight flexion and extension of the toes. Tone much reduced in lower extremities. Level at T₂—4 with secondary level at S₂ for all types of sensation.

Slight papillitis in each eye, pupils equal, regular and central, both sluggish to light and accommodation, left more than right. Right ptosis, right eye immobile; left eye, deficient internal rectus. Partial left seventh.

Straw colored spinal fluid, otherwise laboratory examinations were negative.

Following lumbar puncture the patient developed a total transverse lesion at the level of T₂, complete paraplegia, retention of urine, pneumonia and death. No autopsy.

The following questions submitted to Dr. Riley before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask Dr. Riley this question: Have you seen paralytic spinal types which you could at the time diagnose as due to the virus of epidemic encephalitis and not to that of acute poliomyelitis? I mean, if you had not seen them just at the time of the epidemic, was there anything about those cases to help you at the time to differentiate between the paralytic type of anterior poliomyelitis and the type that is due to the epidemic encephalitis?

DR. RILEY: I think the drowsiness and the cranial nerve systems would be very valuable in differentiating.

DR. SACHS: That is, nothing in the spinal?

DR. RILEY: I do not think so.

DR. TIMME: Dr. Riley, may I ask whether you had any reason at any time to believe that in the ventral poliomyelitic type there were also involvements of the intermedio lateral tract in which the sympathetic cells were either entirely per se involved or in addition to the anterior horn cells?

DR. RILEY: I do not think I have seen any cases that showed that. Usually there was some motor disturbance in connection with the anterior horn manifestations, but I have not seen anything of that alone.

DR. TIMME: Would you be willing to include in your classification the addition of symptoms that would be due to such disturbance of the intermedio lateral tract?

DR. RILEY: I think they should be, but they rarely are in the ordinary routine examination.

DR. TIMME: You think they should appear? Should the classification include that?

DR. RILEY: Yes, I think it should.

DR. DANA: I would like to ask Dr. Riley if he is sure that that last case as reported is a case of encephalitis lethargica. I do not see how that can be a certainty. It is just with a group.

DR. RILEY: The history of some drowsiness, and the cranial nerve symptoms which were quite marked in that case,—both sides were affected, one more so than the other,—and with the other spinal manifestations, the case could hardly be placed anywhere else.

DR. DANA: That is not making a diagnosis. How can you exclude some sort of a mixed infection? It is so entirely different in its course from perhaps 100 cases of epidemic encephalitis.

DR. RILEY: I think that was just the characteristic thing about the disease, as we saw it, that it did not follow any outline.

DR. DANA: That is just the point I think has been too greatly emphasized—the characteristics of exceptional cases. I have seen cases over and over again, and they have a physiognomy that is quite characteristic and distinct. They do not always run to these bizarre forms. You have them and then immediately you form a new type without any post mortem evidence of it. Is there on record, for example, a case like the one you have described—very marked sensory symptoms in which there has been a post mortem which has shown that the case was surely encephalitis?

DR. RILEY: There was another case at the Presbyterian Hospital which was autopsied and showed a symmetrical diminution in the size of the cord and also hemorrhages and destructive processes in the midbrain, etc. It seemed to be quite typical of what we recognize as epidemic encephalitis.

DR. DANA: I am not saying that this is not so, but I am reading a good many of the papers and listening to them, and it always seems as though they were trying to show another bizarre case, and emphasizing extraordinarily unusual types. Moreover, I don't think the cases have always been worked out so as to exclude absolutely some other infection or some mixed infection in those cases.

DR. SACHS: There is one other point I would like to have some information upon for the benefit of the Commission. I may not have understood you correctly, but did you not make a point that in spinal types, we will say, of acute poliomyelitis, there were never cases resembling a transverse myelitis?

DR. RILEY: If I did make that positive, I ought to qualify it somewhat.

DR. SACHS: I remember distinctly, at the time of the epidemic of acute poliomyelitis, having seen such cases which were really typical transverse myelitis. The only evidence that we had that they were of this nature was the unusually rapid recovery, very much more rapid than in any other diseases we had ever seen. I should be glad to know whether from your study of the literature you found that there was no basis for the diagnosis of epidemic

poliomyelitis in these cases, whereas I believe you say there were some in this epidemic. That is, I understood you to claim that there was no reason to suppose that in the epidemic of poliomyelitis any cases of acute transverse myelitis occurred, which could be classified as due to that epidemic, whereas you did think there were some such cases occurring during an epidemic of encephalitis.

DR. RILEY: Yes, that is true. We got that impression from the literature and also from some of these cases. For instance, this last one only developed a transverse myelitis picture after a lumbar puncture, and that is the reason I said that some had considered the transverse myelitis forms as simply the result of an accident in the course of epidemic encephalitis—as a hemorrhage or thrombosis, etc., not as a pure type of disease.

DR. DANA: Then you do say that possibly these definite transverse myelitis pictures may be accidental?

DR. RILEY: Yes, I do not know myself; I am quoting.

PERIPHERAL AND RADICULAR TYPES (FOSTER KENNEDY). It is only for the purpose of presentation of different clinical aspects of epidemic encephalitis by different observers that we have divided with some arbitrariness the disease into different clinical groups. A clinical discussion, under these circumstances, therefore, must begin by a disclaimer that a type is ever a disease of its own genus, and by an assertion that it merely represents a variety in which the virus has fallen with some greater incidence on one part of the body than on another. Of the circumstances which go to permit this variety of form we know little; naturally, disease pictures will vary with the structure affected, and variety in such pictures following nervous lesions is furthered, because from lesions of the nervous system we may have either obliterations of normal functions or release of functions normally controlled by centers higher in the neural hierarchy.

It is probable that variety of clinical form in epidemic encephalitis is often produced by variety of virus or by a constant virus varied by appearing in different evolutionary guises.

However this may be, it is certain that the peripheral

nerves and spinal roots are affected in encephalitis to a considerable degree.

Spinal Root. Abrahamson says that in 60 per cent of his cases unmistakable signs of radiculitis were present. This is a higher figure than has been obtained in the series at Bellevue Hospital; we have been slow, however, to ascribe to root or peripheral infection subjective symptoms unsupported by objective phenomena. Nevertheless, in some cases, the distribution and character of the pains have forced us to the same conclusions; in a few others, sensory changes similar to those found in tabes dorsalis have been present; in a small number there have been localized atrophies of muscles such as would occur from involvement of contiguous anterior roots.

Cranial Nerve. Palsies of single cranial nerves are not uncommon, the seventh and third nerves being those most usually affected. It should be pointed out that the involvement of the seventh nerve in most of our cases has not been accompanied by any defect either of the fifth, eighth or sixth nerves, a consideration which would exclude the possibility of the lesion being in the pontocerebellar angle or in the nucleus of the facial nerve in the pons, and would compel observers to explain the facial palsies in these cases by a lesion of the seventh nerve in its parenchyma.

Peripheral Nerve. Not only were single cranial nerves picked out for damage by the infection, but occasionally single peripheral nerve trunks were involved in similar fashion. An interesting example of this was seen in a riveter who in April of this year began suddenly to have sharp lancinating pains in the arms and shoulders accompanied by much weakness in the upper extremities. When examined, some three weeks after the beginning of these symptoms he was found to have a noticeable loss of power in both serratus magnus muscles, the right scapula being winged on raising the arm on that side. The patient had diplopia, heavy sweating, slowness of emotional initiative and a mask-like facies some four weeks after the development of his peripheral nerve symptoms. It is at least an interesting speculation

whether this man's occupation as a riveter imposing reiterated violent exertion of his serrati and notably of the right muscle could have had any determining effect on the incidence of the disease on the long thoracic nerve.

Symptoms. Several observers, notably Pardee and Barker, have described cases of severe girdling pains beginning in the cervical region with persistent hiccough and descending to the lumbar region and lower extremities. None of their cases had any objective sensory losses, but all had a pleocytosis in the spinal fluid. It is remarkable that herpetic manifestations were not more frequent among such patients; only one of the Bellevue Hospital group had herpes, and that was confined to the left auricle and external auditory canal and was associated with a complete left facial palsy of a peripheral type. A geniculate ganglionitis was in this case the presumptive lesion.

Polyneuritis. Instances of indubitable polyneuritis on an encephalitic basis are less common in the experience of the workers in Bellevue Hospital and the Neurological Institute than are the radicular types or those in which isolated nerve trunks such as the facial are alone involved.

J. D. a watchman, aged fifty-three, formerly a coachman, a man who had never drunk more than an occasional glass of beer, in August, 1920, began to suffer from severe burning pains in the calf muscles, with tingling in the toes and progressive weakness in the legs. He became unable to walk and at the same time had severe headaches and felt very ill. He had a constant pyrexia of about 2°F . After two weeks the same symptoms as had been in the legs were felt in the arms which gradually weakened. A month after these developments he began to see double, his pupils became unequal and sluggish to light, the left face became paresed, the facial expression grew mask-like, he sweated excessively; the sleep mechanism was reversed, that is, he was drowsy by day and wideawake by night, the pulse was persistently about 125, and the sugar content of the spinal fluid and its cell content were greatly increased. There was atrophy in the intrinsic muscles of both hands and fibrillary twitching in all four limbs. All deep

reflexes were abolished. There was excruciating tenderness in the calf muscles and abolition of the sense of position in the feet and hands with consequent sensory ataxia. There was no weakness in speech or swallowing. Micturition was slow and difficult, but there was no incontinence.

This man is making a slow recovery (December, 1920). This case and two others in the Neurological Department at Bellevue Hospital remarkably resembled those reported before the American Neurological Association by Dr. Foster Kennedy under the caption "Acute Infective Neuro-nitis." In them, however, it was unusual to have a cerebral symptom complex, though autopsy examination revealed inflammatory lesions in the peripheral nerves, spinal ganglia and cord and cortex as well; lesions which for the most part, however, diminished as one ascended in one's examination.

These cases occurred as a minor epidemic among soldiers in the field and were accompanied by fever and other evidences of a general infection. In some few the posterior spinal roots were especially affected, so that root zones of grossly altered sensibility were easily demonstrated. A constant feature of these soldiers was the peripheral paralysis of one or both sides of the face, a feature commonly but by no means constantly seen in the American cases of epidemic encephalitis.

In connection with these cases, however, we must consider those cases of acute polyneuritis which occur as a complication of malaria and of enteric fever and scurvy, and perhaps especially those recently described by Farnell in which a staphylococcal gastro-enteritis was promptly followed by acute polyneuritic symptoms with not infrequently fatal results. All these diseases differ from similar conditions found in the encephalitic epidemic in degree rather than in type, but make manifest that disease pictures are sketched and colored more by the varying nature of the structures attacked than by the specificity of the invading virus.

The following questions submitted to Dr. Kennedy before the Commission, together with the answers to them, are here reported *verbatim*.

DR. DANA: Did you have any radicular cases, purely sensory—I mean with intercostal neuralgia and herpes?

DR. KENNEDY: We had one case I mentioned of herpes in which the left face was completely paralyzed with herpes in the external canal, a very definite case which I think was no doubt a geniculate ganglionitis. There have been no other cases of herpes in my experience. One of the cases I describe here had a very definite sensory ataxia with loss of sense of position in the arms. He had other cerebral manifestations of encephalitis lethargica. He had diplopia, mask-like face, heavy sweating, etc.

DR. BARKER: Is it your impression that those cases described as infectious polyneuritis by Bradford and others during the war come under this group?

DR. KENNEDY: I saw those cases, Dr. Barker, and they had the appearance of it, but they had no lethargic manifestations at all, none of them. They had all the evidence of a general infection, but they had no evidence of a midbrain infection. There was one patient I saw whom I have not mentioned in this little abstract—a child who in February of this year came down with vomiting and severe gastric pain, abdominal pain, and a torticollis; saw double and began to lose power in the arms and legs, so much so that the torticollis was of spasmodic nature. There was complete loss of power in the arms and legs in that child and that power fluctuated. There was complete loss sometimes and then for three weeks afterwards there would be a little return of power and then there would be another increase in the abdominal pain and the power was gone again. Both the parents and the doctor told me that it came, as it were, in waves; that almost every four weeks from February until now there was a little remission, but gradually the waves of the involvement of loss of power of the child became less, and the child is now considerably recovering. The recovery between each attack was a little bit more than the next wave would put it back, so that now in December the child is able to walk again and has lost a good deal of its paralysis, but not all. There is a great weakness of the neck muscles so that the head is thrown forward; the knee-jerks are not returned yet; the ankle-jerks are returned.

The same condition of rapid wave-like attacks of the disease was seen during the war. I would examine a soldier at eight o'clock one night and find definitely that he could not feel below the mid thigh, and I would find twelve hours later that he could feel only below the ankle—a condition which I could not understand. I noticed that one of the pathologists suggested that the essential lesion in some of these cases was an edema, flooding the nerve tissue and inhibiting conduction. The clinical manifestations that I have seen in some of the encephalitis cases and in those cases to which you refer, Dr. Barker, made me believe that they might be explained by an edematous phenomenon, and of course one would point out in that connection that sclerosis very often behaves in a similar fashion.

DR. BARKER: Might I ask also if there have been sensory forms due to neuritis with spontaneous pains as a characteristic feature and taken by the practitioner at first to be infectious arthritis or myositis, often referred to orthopedists?

DR. KENNEDY: I have seen those cases, but I do not think I have seen them having that sad conclusion.

DR. WEISENBURG: I would like to ask if Dr. Kennedy has seen cases in which the pains were limited to certain parts of the body only? For example, I had one patient to whom the pains were limited to the parts above the line of umbilicus and never below.

DR. KENNEDY: We have a patient in Bellevue Hospital at present whose pains are confined to the arms. That woman became affected in February of this year and she has complained of pain ever since. I can't find there are any objective changes oddly enough in all that time in her arms, but she complains of excruciating, burning pain down the arms in the lower segment distribution.

DR. DANA: How are you going to exclude, as the cause of these so-called radicular pains and paralyses, the conditions of the spinal cord or of the cerebral tissue itself? Why do you say a person has a shoulder pain or facial pains? Facial pain may be ophthalmic pain, may it not?

DR. KENNEDY: Facial pain might be an irritation easily enough of the nucleus of the fifth nerve.

DR. DANA: Is there any way of differentiating between so-called radicular pains and paralyses and edematous conditions of the anterior or posterior horns of the spinal cord?

DR. KENNEDY: No, sir, I do not think so. There is evidence that hemorrhages have been found in the posterior ganglia in some cases. That being so one argues that certain other clinical cases which correspond to them in type may have some of the lesions.

DR. PATRICK: You spoke of a case of hiccough. I should like to inquire whether you know that that was a real hiccough—or a spasm of the abdominal muscles? I believe, Dr. Kennedy, you quoted that from someone else.

DR. KENNEDY: That is Dr. Barker's case.

DR. SACHS: Has anyone as yet seen the cases of hiccough that are reported as being connected with epidemic encephalitis?

DR. TIMME: We will ask Dr. Barker to answer.

DR. BARKER: Let me say that I have seen 2 cases of hiccough, described by the practitioners, lasting a long time, and they seemed to be definitely those of epidemic encephalitis. Several epidemics of hiccough were reported as occurring at the same time as the epidemic of encephalitis. One such case was examined roentgenoscopically, and there was no movement in that case other than contractions of the abdominal muscles. That was an abdominal muscle hiccough rather than diaphragmatic, but that is the only case I know of trying to differentiate. I rather think these hiccoughs are associated with the epidemic.

DR. TIMME: Perhaps Dr. Hunt could answer something from his observations in his myoclonic types involving abdominal muscles—whether that is an intensive type of this form.

DR. HUNT: In none of my cases was there anything that simulated a hiccough. It would have been very defective observation that would have interpreted any of the movements as related to hiccough, but I could imagine that with a very rapid, definite, rhythmical movement of the upper abdomen it might simulate the real hiccough, but that was not so in my cases.

THE SEROLOGY OF THE SPINAL FLUID AND BLOOD IN EPIDEMIC ENCEPHALITIS* (WALTER M. KRAUS AND IRVING

* The material for this article was obtained from records of certain New York Hospitals: Bellevue, Mt. Sinai, The Neurological Institute, New York, Presbyterian, Roosevelt and St. Luke's, and from the following physicians: James B. Ayer, Boston; Lewellys F. Barker, Baltimore; Peter Bassoe, Chicago; Josephine B. Neal, New York; Harry C. Solomon, Boston; Walter F. Schaller, San Francisco; E. W. Taylor, Boston, and Lloyd J. Thompson, Boston.

H. PARDEE). The subject matter which we present has, for the sake of clearness, been divided into three parts; the first contains a review of the literature, the second data, based on the 245 case reports obtained from the foregoing sources, and the third, a section devoted to differential diagnosis by means of the blood and spinal fluid serology.

Review of the Literature. Until the publication, in 1917, of the description of the first cases of epidemic encephalitis in Vienna, no reliable statistics of the changes in the blood and spinal fluid in this disease were obtainable. At this time, von Economo¹ gave an account of the clinical and laboratory findings which we shall consider the first accurate data on the subject. He pointed out the following changes in the spinal fluid: An excess of globulin was found and the spinal fluid cell counts ranged from normal to 43. The fluid was clear and, in some cases, under pressure. The only group of observations which were not mentioned by von Economo concerned changes in the quantity of sugar in the spinal fluid. His observations on the colloidal gold curve were summed up in a sentence. No curves were given. In this country, curves were first published by Josephine B. Neal² in September, 1919. She mentioned the abnormal changes and the similarity to those curves found in acute anterior poliomyelitis. Following this, observations on the occurrence of syphilitic and paretic types of curves were made by Bassoe,³ Brill and Benson,⁴ Davis and Kraus,⁵ and Archambault.⁶

¹ Von Economo. Encephalitic lethargica. *Wien. klin. Wchnschr.*, 1917, xxx, 581.

² Neal, Josephine B. Lethargic encephalitis. *Arch. Neurol. & Psychiat.*, September, 1919, ii, 271.

³ Bassoe, P. Epidemic encephalitis (Nona). *J. Am. M. Assn.*, April 5, 1919, lxii, 971.

⁴ Brill and Benson. Lange reaction in epidemic encephalitis. *J. Lab. & Clin. Med.*, June 20, 1920, v, 113.

⁵ Davis and Kraus. The colloidal gold curve in epidemic encephalitis. *Am. J. M. Sc.*, 1921, clxi, 109.

⁶ Archambault, La Salle. Choreo-athetoid and choreopsychotic syndromes as clinical types or sequelæ of epidemic encephalitis. *Arch. Neurol. & Psychiat.*, November, 1920, iv, 484.

The foregoing gives an idea of the chronological order of the description of the spinal fluid findings. The following paragraphs will be devoted to a detailed account of the spinal fluid and blood findings given in the literature.

A. Spinal Fluid: Appearance. In the greatest majority of cases, observation records a clear, colorless fluid. Bloody fluids have occasionally been found, in fact more commonly than could be accounted for by the puncture of a vein. A xanthochromiac appearance has been extremely rare.

Pressure. The pressure of the spinal fluid varies from normal to a considerable increase.

Cell Counts. In spite of the fact that von Economo in his original description made note of a pleocytosis, the French, who had studied the matter carefully during the years 1918-1919, had come to the conclusion that a normal cell count was a rule and of diagnostic importance. It was not until December 10, 1919, when Bénard¹ reported a case with pleocytosis, that doubt was thrown on the invariability of normal spinal fluid cellular content in epidemic encephalitis. The absence of pleocytosis before this date, as noted by the French, was not found by the British and American observers. The latter published cases seen in 1919, in which there appeared more than the normal number of cells. The cells which appeared in the spinal fluid were always predominantly of the mononuclear type although polymorphonuclear increase up to 15 per cent had been found in many cases.

The impression gathered from the literature is that the number of cells may vary from normal to an increase of several hundred.))

Globulin. The discrepancy between the report of the French, who noted an absence of globulin in the early cases of the epidemic, and the English and Americans who had

¹ Bénard, R. Le liquide céphalo-rachidien dans l'encéphalite léthargique. *Paris med.*, June 5, 1920, x, 474. (This article contains a thorough review of the French literature up to June, 1920. References from the literature of other countries are also given.)

reported its presence in increased amounts, is a parallel to the reports on the cell counts. In general, it may be said that an increase in globulin occurs in the majority of cases.

Sugar. No report of the amount of this substance was made until the end of 1919. From that time until the present, the French have published fifteen observations on the amount of this substance in the spinal fluid. These varied from 0.067 per cent to 0.106 per cent, averaging 0.085 per cent. It would seem, therefore, that the amount of sugar in the spinal fluid, wherever it has been reported, has exceeded the normal quantity.

Wassermann Reaction. This has been found negative in the spinal fluid whenever it has been reported except in syphilitic cases.

Colloidal Gold Reaction. Von Economo commented briefly on the reaction of colloidal gold solutions as follows: "The gold-solution reaction shows no typical elevation of its curves." This implies that some changes existed.

B. Blood: The white blood counts, as reported in the literature, reveal a variation from 3,000 to 25,000, the average being about 15,000. Slight polymorphonuclear increase is the rule. The remainder of the blood picture is normal. Observations on the blood chemistry have been scattered and incomplete. The blood Wassermann reaction is reported negative.

THE EVIDENCE OF CASE REPORTS

The general statistics in Table I give a numerical summing up of the case reports on which we base our data.

TABLE I.—NUMERICAL SUMMING UP OF CASE REPORTS

Number of cases.....	245
Number of spinal fluid cell counts.....	260
Number of spinal fluid globulin determinations.....	214
Number of spinal fluid sugar determinations.....	12
Number of spinal fluid colloidal gold curves.....	120
Number of spinal fluid Wassermann tests.....	185
Number of blood Wassermann tests.....	161
Number of blood polymorphonuclear counts.....	171
Number of blood differential counts.....	153

A. *Spinal Fluid*: As a rule, the spinal fluid shows considerable and important changes in epidemic encephalitis. These are extremely variable, not only in different cases, but also in the course of each case. The most characteristic changes are:

1. A clear, colorless fluid.
2. An increase in the pressure of the cerebrospinal fluid when withdrawn.

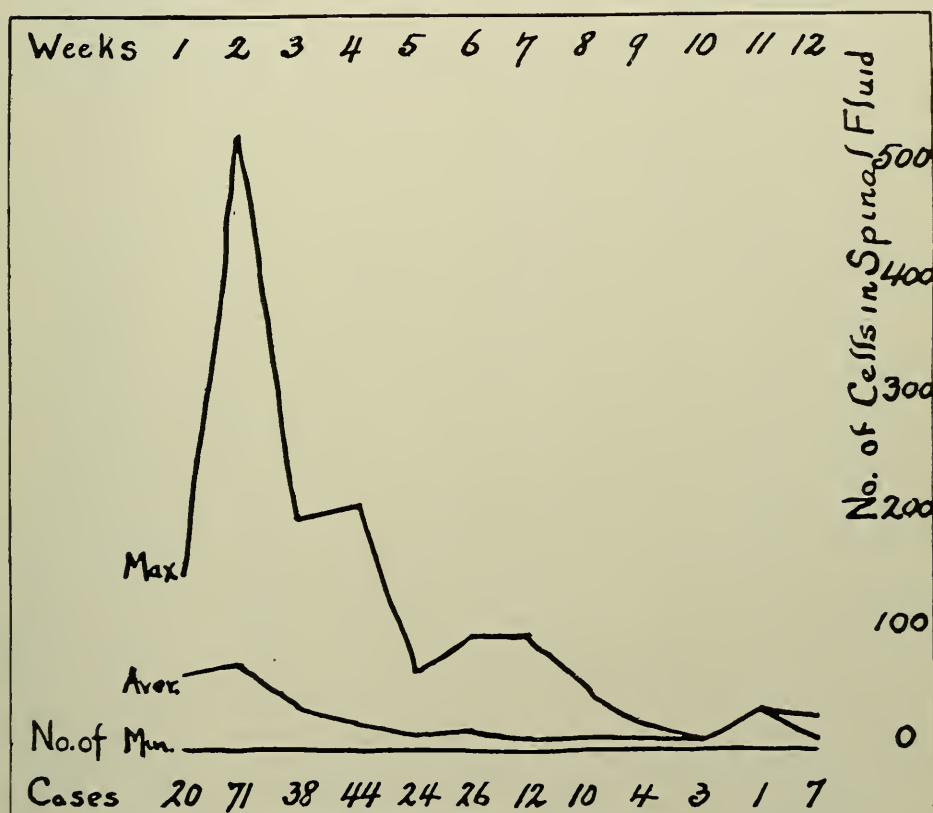


FIG. 6. Variation in the number of cells in the spinal fluid.

3. An increase in the number of mononuclear cells.
4. An increase in the amount of globulin.
5. An increased amount of spinal fluid sugar.
6. A negative Wassermann reaction.
7. The presence of bodies producing a change in the color of a solution of colloidal gold (Lange reaction).

1. *Appearance.* The fluid is, in most cases, clear and colorless. Occasionally bloody fluid is obtained.

2. *The Pressure.* As would be expected, the pressure of the spinal fluid is sometimes very much increased. Here also no rule exists, and, though this hypertension is frequent, it is not universal.

3. *The Cell Count.* Table II indicates the minimum, maximum and average number of cells during each of the first

TABLE II.—NUMBER OF CELLS IN THE SPINAL FLUID

WEEKS	MINIMUM	AVERAGE	MAXIMUM	CASES
1	2.0	63.3	160.0	20
2	0.0	71.0	540.0	71
3	0.0	37.3	200.0	38
4	0.0	28.2	222.0	44
5	1.0	21.3	70.0	24
6	0.0	25.7	100.0	26
7	1.0	21.0	101.0	12
8	2.0	16.2	48.0	10
9	0.0	13.0	32.0	4
10	5.0	8.0	14.0	3
11	4.0	40.0	40.0	1
12	2.0	15.2	33.0	7
MONTHS				
4	4.0	40.2	108.0	9
5				
6	3.0	32.0	61.0	2
7	...	2.0	1
8	2.0	2.5	3.0	2
9				
10				
11				
12				
13				
21	...	2.0	1
24	...	3.0	1

TABLE III—B. NUMBER OF CELLS IN THE SPINAL FLUIDS AT VARIOUS MONTHS INCLUDING REPETITION OF CELL COUNTS*

	Months					
	4	5	6	7	8	24
4		{ 3 }	3	2	2	3
6		{ 5 }	61	..	3	..
7		{ 9 }	..			
10		5		
14		5				
15		8				
98		22				
100		..				
108						

* Except where repetitions occur, the figures are arranged in an ascending order. Bracketed figures indicate several observations on the same case and in the same week.

twelve weeks and during the fourth to twenty-fourth months of the disease. The graph in Fig. 6 presents this in a different way. It may be seen that, on the average, more cells are found during the first three weeks of the disease. The value of this in individual cases is diminished by the variations in the number of cells in each week. An idea of this may be had from an examination of the columns showing maximum and minimum number of cells for each week and also from Table III. The number of polymorphonuclear cells may be as great as 15 per cent.

Fluctuation in the number of cells occurs during the course of the disease. When there is a remission, the cell counts may increase.

4. *Globulin.* The globulin is usually increased to a moderate degree (in 72 per cent. of the cases). However, since this is not always true, its diagnostic value in individual cases is lessened. The presence of globulin is not always paralleled by the presence of cells or a positive colloidal gold curve.

5. *The Sugar Test.* The majority of the tests have been done at Bellevue Hospital since May, 1920. No estimates were given in case reports outside of New York.

The number of estimations is insufficient to enable us to draw any but tentative conclusions. However, those figures which we have, show, without exception, values above normal.

The sugar content of the spinal fluid has been tested in 12 cases. It has ranged from 0.062 per cent to 0.095 per cent (Table IV).

TABLE IV
SUGAR CONTENT OF SPINAL FLUID IN TWELVE CASES

WEEK	MONTH	PERCENTAGE OF SUGAR IN THE CEREBROSPINAL FLUID
3	..	0.082
3	..	0.075
6	..	0.068
9	..	0.062
9	..	0.094
..	4	0.065
..	4	0.080
..	4	0.094
..	4	0.092*
..	5	0.070*
..	5	0.063
..	10	0.095

* Observations on the same case.

6. *The Wassermann Test.* This was negative when reported.

7. *The Colloidal Gold Curve.* This has been found changed in 100 out of 120 cases (83 per cent). The type of curve varies considerably, as Figure 7 shows. There is a tendency toward elevation of the left-hand part of the curves in the later stages of the disease, but this is not constant. Positive curves were found as late as the twenty-first month. Elevations of the right end of the curve alone were not found.

The tendency is to a color change in the high and medium concentrations of spinal fluid. Changes in the low concentrations do not occur alone, but may occur when the medium and the high concentrations are altered.

B. *Blood:* Normal values for red blood count and hemoglobin have invariably been found. Leukocyte counts have varied from a minimum of 4,500 to a maximum of 32,000,

the general average being 12,000. Figure 8 shows these relations in graphic form.

Maximum, minimum and average percentage of polymorphonuclears are shown in the graph in Figure 9. This will

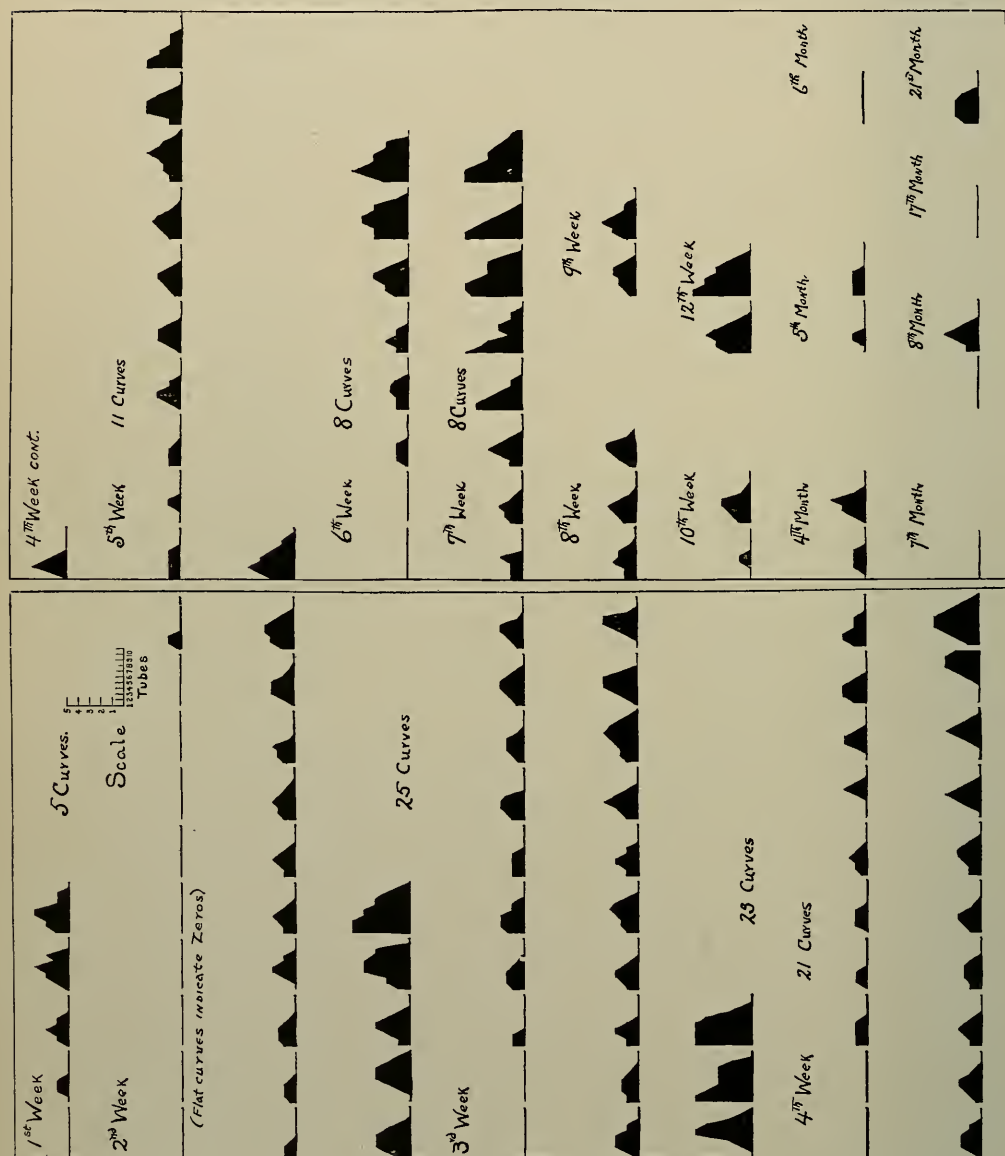


FIG. 7. Colloidal gold curves.

serve to emphasize the extent of the variations in the various stages of the disease.

The number of observations on the chemistry of the blood are too few to enable us to draw any conclusions.

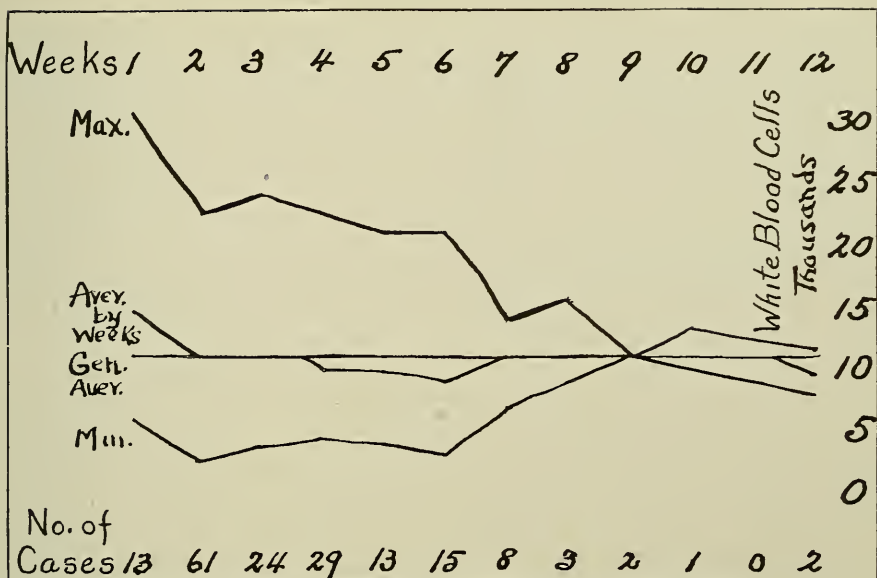


FIG. 8. Variation in leukocyte counts in the blood.



FIG. 9. Variation in numbers of polymorphonuclears in the blood.

A few observations (12) on the amount of sugar in the blood have been recorded and are within normal limits. They are recorded in Table V.

TABLE V

PERCENTAGE OF SUGAR IN THE BLOOD IN TWELVE CASES

WEEK	MONTH	PERCENTAGE OF SUGAR IN THE BLOOD
2	..	0.095
2	..	0.075
3	..	0.100
3	..	0.100
3	..	0.111
3	..	0.083
4	..	0.120
5	..	0.100
..	4	0.110*
..	5	0.170*
..	6	0.143
..	7	0.101

* Observations on the same case.

Wassermann Reaction. The Wassermann reaction has been found negative when reported.

Differential Diagnosis. 1. Other forms of meningitis: (a) serous; (b) acute purulent; (c) tuberculous; (d) syphilitic meningitis and neurosyphilis.

2. Acute anterior poliomyelitis.
3. Brain tumor.
4. Parkinson's syndromes and allied conditions.
5. Multiple sclerosis.
6. Polyneuritis.

In order to use the serology of the spinal fluid in epidemic encephalitis for the purpose of differential diagnosis, it is necessary to make observations on the pressure, the cell count, the globulin, the presence of sugar, the colloidal gold

curve and the Wassermann reaction. When these observations give no conclusive evidence, a quantitative estimate of the sugar of the spinal fluid should be made.

The various examinations mentioned above will, in the majority of instances, serve to differentiate epidemic encephalitis from other diseases clinically similar. Certain diseases, as will be emphasized in the following paragraphs, cannot be differentiated by all of these means.

1. MENINGITIS: (a) *Serous Type (Meningismus)*. The cells and globulin in this disease show no deviation from the normal, but the pressure is always increased. These facts do not serve as a differential point for there are some cases of encephalitis in which the picture is the same.

(b) *Acute Purulent Meningitis*. In the early stages, the marked polymorphonuclear increase is the most important differential point. In the later stages, the presence of cloudy opalescent fluid, with cellular increase of several thousand cells, predominantly of the polymorphonuclear type, present a picture which is never found in epidemic encephalitis. The quantitative sugar is usually decreased or absent, and the colloidal gold solution may show a color change in the higher dilutions (right end of the curve). Bacteriologic examination may reveal organisms by smear or culture.

(c) *Tuberculous Meningitis*. Examination of the spinal fluid, as thoroughly as has been suggested in the opening paragraphs, must be made in order to differentiate this disease serologically from epidemic encephalitis. It is emphasized in the literature that in tuberculous meningitis the cell count has a tendency to increase during the progress of the disease, while in epidemic encephalitis this is not the case. This observation, in our opinion, is of considerable importance, but we do not believe it to be invariably correct since there are cases of epidemic encephalitis in the course of which the cell count rises (Table III). The picture of the spinal fluid in epidemic encephalitis may be identical with that of tuberculous meningitis with one important excep-

tion—the quantitative sugar. This is almost invariably diminished in the latter disease.

The colloidal gold curves seen in tuberculous meningitis are similar to those found in epidemic encephalitis, with the possible exception of paretic types of curves. No observations on the presence of these in tuberculous meningitis have been found. They are fairly common in cases of epidemic encephalitis.

(d) *Neurosypilis and Syphilitic Meningitis.* Epidemic encephalitis may be ruled out by a positive Wassermann reaction in the blood or spinal fluid, except in the rare coincidences of the two diseases. In such cases no differentiating point can be made. In cases in which the Wassermann reaction is not positive in the spinal fluid the other findings are of no value when the history or clinical findings are clearly indicative of syphilis.

2. *Poliomyelitis.* This disease presents a picture which cannot be differentiated (at the present state of our knowledge) from epidemic encephalitis, in so far as the spinal fluid is concerned. Further researches on immunologic tests and quantitative sugar estimation on the spinal fluid may yield data of differential diagnostic importance.

3. *Brain Tumor.* The presence of a high cell count is of extreme rarity in brain tumor; other than this there are no differential points in the diagnosis from epidemic encephalitis, in so far as the spinal fluid is concerned. In brain abscess, a mild pleocytosis, usually of polymorphonuclear cells, is often found.

4. *Parkinsonian and Allied Conditions.* Since the occurrence of the recent epidemic of encephalitis, this group must be divided into two parts: those caused by encephalitis and those not caused by this disease. In the acute and chronic stages of both of these groups, the spinal fluid findings are of great differential diagnostic importance. When the condition is due to encephalitis, several or all of the findings described in the foregoing may be found. When in this group a positive Wassermann reaction is found, the history of the case

will decide the diagnosis rather than the spinal fluid findings, and the probability is that the case is due to syphilis. The Parkinsonian syndrome may be on a syphilitic basis. When the condition is not due to encephalitis or syphilis, the spinal fluid is negative.

5. *Multiple Sclerosis*. The differential diagnosis between this disease and epidemic encephalitis is, in our opinion, as far as the spinal fluid is concerned, not possible.

6. *Polyneuritis*. As there are no changes in the serology of the fluid in polyneuritis, while in most cases of epidemic encephalitis some change is found, this fact will serve as a differential point.

Conclusions. The spinal fluid findings in epidemic encephalitis have led us to certain general conclusions in regard to the nature of the disease.

The course of the disease, as illustrated by the serology of the spinal fluid, is extremely variable. A mild insidious or chronic type lasting for months exists, as is shown by the continuation of abnormal changes in the spinal fluid over long periods of time. An acute, fulminating type also exists and may or may not show serologic changes in the spinal fluid. Midway between these two extreme types of the disease is a combination of the acute, fulminating and chronic insidious types. In this type the spinal fluid findings indicate an active process which, after several weeks, subsides, leaving few or no serologic changes. Then the process lights up again with recrudescence of abnormal fluid findings, and may then continue to a fatal ending or what appears to be a recovery. It is striking that patients who have died have not, as a rule, shown any marked aggravation of the spinal fluid changes before death. The reason is that death occurs from an involvement of vital centers, which is not dependent upon a meningitis.

The low average of cell counts found in this disease indicates that the meninges are very little involved in the pathologic processes, the point of attack of the infection being

predominatingly through the vascular and lymphatic systems. The meninges are not directly attacked.

The increase in the spinal fluid sugar, which has been noted whenever tests of this kind have been made, has appeared to us to be of great interest. This has been attributed to an involvement of the center of Claude Bernard in the floor of the fourth ventricle. However, it has also been shown by Aschner¹ that "puncture of the floor of the third ventricle causes intense glycosuria." This arouses doubt in our minds as to the validity of the hypothesis that the hyperglycorrhagia is necessarily due to a lesion of the fourth ventricle.

Furthermore, we have been impressed by the lack of correspondence between the amount of spinal fluid sugar, which is always increased, and the amount of blood sugar, which is never increased (Tables IV and V). This leads to an hypothesis which must be considered in seeking an explanation for the quantitative sugar changes. The pathologic picture of epidemic encephalitis is essentially one of the blood-vessels and the perivascular spaces. It seems possible that the thin membrane of cells, which normally retains within the blood a greater amount of sugar (0.80 per cent to 0.120 per cent) than that of the spinal fluid (0.040 per cent to 0.060 per cent) may, by being injured, permit the amount of sugar in the spinal fluid to approach that of the blood.

The occurrence of rapid emaciation during the encephalitic process and of marked adiposity after it strongly suggests metabolic disturbances dependent on endocrine dysfunction. We believe that the observations on the relations of striate lesions to creatinism, the presence of cirrhosis of the liver in progressive lenticular degeneration (Wilson's syndrome), and of genital dystrophy, similar to Frölich's syndrome, occurring in midbrain lesions, are of great importance from both a theoretic and, perhaps, a clinical point of view. A hypothalamic—vegetative nervous system—endocrine connec-

¹ Aschner, B.: *Zur Physiologie der Zwischenhirns*, *Wien. klin. Wchnschr.*, 1912, No. 25, p. 1042. Quoted from H. Higier: *Vegetative Neurology*, *Nerv. & Ment. Dis.*, Monograph Series, 1919, No. 27, p. 35.

tion, seems possible. We should like to urge an investigation of the basal metabolism as well as chemical blood examinations in cases of epidemic encephalitis in the hope of obtaining more definite data on this very little considered subject.

The diagnostic value of the spinal fluid findings in epidemic encephalitis is mentioned in detail in the section on differential diagnosis. The combination of an increase of cells, globulin and sugar with changes in the colloidal gold curve constitutes a tetrad of laboratory findings of diagnostic importance. Findings other than these are not of diagnostic importance unless related to the clinical findings.

The blood picture gives evidence of a type of infection which does not call forth a polymorphonucleosis. It does not differ essentially from the picture shown by other similar toxemias and is mostly of importance in differentiating from organic diseases of nontoxic origin, such as brain tumor.

The following questions submitted to Dr. Kraus before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TILNEY: Dr. Kraus, what in your opinion is the most important single feature in the spinal fluid making the diagnosis of epidemic encephalitis?

DR. KRAUS: At the present state of our knowledge of the various tests which can be done on the spinal fluid, the most important thing, I think, is the quantitative sugar determination. I should like to qualify the answer by saying that there have been very few if any reports in the literature about the spinal sugar in other diseases, so that the conclusion has to be made with reservations.

DR. DANA: Have the authors found that meningitis reactions in the fluid are added to the encephalitis after frequent lumbar puncture?

DR. KRAUS: We have been unable to make any observations on that point.

DR. AYER: What does the differential cell count in spinal fluid show?

DR. KRAUS: We attempted to clear up that point but haven't been able to do it quite satisfactorily. It seems that at the begin-

ning of the disease there is a tendency for the number of polymorphonuclears to be much greater than at the later stages of the disease, and Dr. Pardee in reading the paper mentioned the fact that at the beginning of the disease about 15 per cent of polymorphonuclears are very frequently present, but we have not been able to get the time relations of the cell counts in a sufficient number of cases to warrant our making that a definite conclusion. That seems the general tendency.

DR. SACHS: For how many weeks of the disease would the sugar test be of importance according to your experience?

DR. KRAUS: During the entire disease. I have recently seen a case beginning in February, 1920, a definite case, which showed a sugar content of .95 about two weeks ago (December, 1920).

DR. DANA: Do I understand that you found no particular differences in the cell count as a result of frequent repeated lumbar puncture?

DR. KRAUS: We noticed no such occurrence. We did not notice any change whatsoever in going over the statistics which we had on hand from case reports. We had not thought of that point particularly, but nothing in that connection struck us in going over it.

DR. DANA: Were not there a good many cases under observation where repeated lumbar punctures were done?

DR. KRAUS: Of the cases which we saw, I should say that probably 40 cases or 50 cases had repeated punctures, and of that number not more than 10 perhaps showed an increase. Whether that was due to the number of lumbar punctures or due to change of condition of the brain due to infection, I am unable to say.

DR. TAYLOR: Dr. Sachs and I did not quite understand the colloidal charts.

DR. KRAUS: The little mountain represents the change in the color, and the millimeter paper is so arranged that one millimeter in the horizontal direction is equal to one tube. Two millimeters in the vertical direction equal a change of say from one to two, or two to three, or three to four in color change.

DR. TAYLOR: Can you tell us briefly what the characteristic curve is?

DR. KRAUS: There is no really characteristic curve in any point of the disease as far as we were able to determine it. The so-called paretic type occurs quite frequently and the type of low curve

running right through suggesting a meningitic type occasionally occurs. We were unable to determine any definite type in any of these cases in relation to time, to the duration of the disease, the intensity or any other factors.

DR. TAYLOR: In regard to pressure, did you tabulate the pressure carefully? Did you measure it in millimeters or was it an assumption?

DR. KRAUS: It was an assumption from observation; it was not measured.

DR. PATRICK: May I inquire if you have done any sugar determinations in recovered cases after the symptoms have disappeared?

DR. KRAUS: No, sir, because we have never seen recovered cases. As a matter of fact the sugar determinations that we have made were only done in May and we did not have much opportunity in the summer to have very many made, which accounts for the paucity of the observations.

CONCLUSIONS OF THE COMMISSION

The Commission submits that spinal, radicular and peripheral nerve involvements in epidemic encephalitis are common, though seldom in absolutely clear-cut forms, and usually accompanied by properly speaking encephalitic symptoms. It would be a repetition of the above reports to enumerate reasons for these conclusions in a clinical domain.

The spinal type of the disease falls into two forms: the ventral poliomyelitic form and the transverse myelitic form. The former is subdivided into two types, an irritative type and a paralytic type. The irritative type is characterized by movements of the spinal level variety, namely, myoclonic and fibrillary.

The irritative type of spinal involvement cannot be entirely differentiated from a radicular localization, which is, strictly speaking, non-spinal. Besides the radicular type of epidemic encephalitis, there is the form with definite peripheral nerve involvement.

The clinical observations to date are almost entirely confined to motor and sensory phenomena. The behavior of the

sympathetic nervous system, especially in relation to tract implications, in the true spinal types remains to be worked out.

The conclusions in the laboratory field are clearly stated and they are considered properly evaluated in the report itself on this phase.

CHAPTER IV

SYMPTOMATOLOGY: PSYCHOTIC MANIFESTATIONS OF EPIDEMIC ENCEPHALITIS

THE material of this chapter is reported by Drs. George H. Kirby and Thomas K. Davis of New York City, and by Dr. Leslie B. Hohman, of the Phipps Psychiatric Clinic, Johns Hopkins University. This chapter deals entirely with the psychotic manifestations of lethargic encephalitis. Dr. Kirby's and Dr. Davis' material is from the institutions of New York State and from the hospitals of New York City. Dr. Hohman's material is from the Phipps Psychiatric Clinic of the Johns Hopkins Hospital.

PSYCHIATRIC ASPECTS OF EPIDEMIC ENCEPHALITIS (GEORGE H. KIRBY AND THOMAS K. DAVIS). The clinical material available for this study comprises 18 cases divided between general hospital patients and patients observed in hospitals for the insane. They are all cases about which we feel there can be no doubt as to the diagnosis of epidemic encephalitis. In each case we were able to get a fair anamnesis, and in those patients who have left the hospitals we succeeded in obtaining information as to the further course and outcome.

The wide variety of terms used by other writers to designate the more striking psychotic manifestations of encephalitis indicates a lack of any generally accepted nosological viewpoint. Few observers have offered any systematic psychiatric grouping of the cases studied. Some ignore the mental aspect of the disease and adhere to a strictly anatomical classification, while others group their cases partly from the anatomical and partly from the psychiatric standpoint.

It is now known that epidemic encephalitis is an acute or subacute inflammatory disease of the central nervous system. It is probable that the disease is caused by an infectious organism. It seems reasonably certain that, as a result of the activity of the causative agent or a toxin, a varying degree of temporary or permanent damage to the cerebral tissues takes place. As a consequence, psychic disturbances of varying degrees of intensity arise.

The psychiatric problems of epidemic encephalitis would, therefore, appear to lead directly to a consideration of those types of mental disturbance capable of being called forth by toxic or infectious causes which act deleteriously on the central nervous system. From the standpoint of clinical differentiation the first question might be, What are the known characteristics of mental disorders arising on such an etiological basis?

The studies of Meyer, Bonhoeffer, Hoch and Bleuler have shown that disturbances of mental function, like disturbances of other functional mechanisms, take place in a relatively limited number of ways. Clinical studies have in fact made it possible to circumscribe a fairly small number of abnormal mental reaction types which are now recognized to be of fundamental importance in all questions of pathogenesis and symptomatology of mental disorders. So far as we can see at present, there are three mental reaction types which are of special psychiatric significance. These are: (1) the organic reactions; (2) the affective reactions; and (3) the trend reactions.

It is our view, based on pathology and probable etiology, and also on clinical experience, that the psychiatric problems of epidemic encephalitis belong essentially in the realm of the organic, more specifically the toxic-infectious mental reaction types. The present study is a clinical contribution in affirmation of this conception.

The features common to all psychoses which develop as a result of brain disease, or injury through trauma, infection, poisons, etc., constitute the organic syndrome. The organic

mental reaction may be acute or chronic. The essential elements of the chronic reaction, encountered in all of the slowly progressive organic brain diseases, are well known. These are impairment of mental grasp, difficulty in activation of memories, defects in orientation and retention with variability in mental capacity and fluctuations in the level of attention, the so-called mental tension defect.

The acute organic reactions have recently become better understood, chiefly as a result of Bonhoeffer's work on acute Korsakoff's disease, and deliria accompanying physical diseases. The typical acute organic reactions are the deliria due to trauma, alcohol, uremia, infections, bacterial toxins, etc. Brain torpor, somnolence or stupor may, however, be the most striking clinical expression of the reaction replacing or alternating with the delirium. In the acute reaction there is difficulty in mental grasp and interference with the elaboration of impressions often to the point of clouding of the sensorium; also orientation and retention defects, and a striking variability in the level of consciousness; when lowered, the train of thought becomes fragmentary; there is then muttering and incoherence. With clouding of consciousness, dream-like ideas and hallucinations appear and there is a marked tendency for habitual trends of thought and activities to dominate the scene—the well-known occupation delirium.

The more common clinical manifestations of the acute organic reactions, as they occur in psychiatric practice, are:

1. Acute delirium: the organic features of which are plainly evident.

2. States of psychic torpor: various grades of mental dullness, somnolence, stupor or coma.

3. Amnestic-confabulatory complex: acute Korsakoff syndrome.

4. A group of more complicated psychotic reactions in which organic elements are combined with emotional disorders, trends and psychomotor disturbances not usually seen in the more typical organic syndromes. In these more

complex cases the personality traits and various psychogenic reactions come more to the front and thereby give a special cast to the clinical picture.

A wide range of neurological syndromes was encountered in our series of cases, but we were not able to make any correlation between physical types and the form or outcome of the mental disturbance. In the following we give a brief analysis of the psychotic symptoms most prominent in epidemic encephalitis.

Sleep Disturbance. Pathological sleep has a wide occurrence in neuropsychiatric conditions; the various cerebral and other conditions with which it is often associated need not be enumerated. In encephalitis a sleep disturbance is the most obvious mental alteration, and we found in all our cases a period of pathological drowsiness at some stage of the disease. The sleep disturbance is best put in terms of hyper- and hypo-function, for in this way it will be quickly brought to mind that not all cases of encephalitis show somnolence. On the hyperfunction side it is serviceable to recognize four gradations: drowsiness, lethargy, stupor and coma. The differences are those of degree. A very striking feature of the lethargic states is the ease with which the patients may be usually aroused and the brightness and alertness then often shown. Such a reaction is not so frequently seen in other toxic-organic somnolent states, but even in encephalitis it is apparently a question of degree or depth of the disturbance, as stuporous patients very often cannot be aroused or if they can be, they show plainly that they are unclear or confused.

Certain cases in an immobile state, with mask-like facies, mutism and open eyes, emphasize the fact that the sleep disturbance, so-called, is only partly an alteration in the level of consciousness and that with it there is an activity disturbance. (This will be referred to again under motor phenomena.)

Hyposomnia or insomnia, noted by some as an onset symptom, occurs in a majority of cases later, if at all. It

is frequently accompanied by an intense psychic overactivity.

Hypersomnia and hyposomnia may alternate in the same patient through a definite day and night cycle with a reversal, however, of the usual order.

The various theories advanced to explain the causation of the alterations of sleep do not adequately account for all the clinical features encountered in our cases, particularly the alternating combinations of hyper- and hyposomnia.

Delirium. The second most common feature of the mental picture is delirium. The delirium of encephalitis presents the general characteristics of an acute organic disturbance. It is usually not prolonged and may in fact be limited to fleeting delirious episodes, especially at night. Transient delirious features during lethargy or stupor may be easily overlooked. The content of the delirium tends to center about habitual trains of thought and the usual daily activities of the patient, while in some instances it is determined by disagreeable somatic sensations. Combined hallucinations and illusionary falsification of things in the immediate environment are prominent. The recollection of the delirious trains of thought may be quite well preserved upon recovery while there is partial or complete amnesia for external events.

Emotional Reactions. The extremely wide range of emotional reactions met with indicates that the differences between individual cases are very great or that the mood varies markedly through the different stages of the disease.

In the early stages, before the onset of the torpor or delirium, marked mood changes were not often encountered. Pronounced depression is not frequent at the beginning. Euphoria and overactivity are at times present at this stage, but they are more apt to be a later development, following the delirium or stupor. Euphoria with added features of a manic state occurs and furnishes a picture not distinguishable from a manic-depressive excitement.

In the lethargic and stuporous phases the most charac-

teristic emotional state is apathy, which may be extreme. However, just as a patient may be aroused from the sleep, so may he usually be aroused by strong emotional stimuli to show an appropriate affective reaction.

We have also observed peculiar, and in a sense contradictory, emotional reactions in patients still unrecovered; one patient exhibits a markedly apathetic state which is spontaneously interrupted by singing and jig-dancing; another patient in a suicidal depression, talks of being killed, yet she can be easily induced to smile or laugh a little. This emotional lability seems not to be fully under her control and the patient has remarked that she knows it is "foolish" to smile. These unusual mood reactions in certain cases suggest, at least superficially, a lack of correspondence between the affect and ideas expressed. We have not found, however, dissociation of affect such as occurs in schizophrenia. It is rather the quick change of mood that is misleading, but with these changes there seems to be always a corresponding change in ideational content.

What appears to us to be a very significant observation is the persistence, in a large majority of cases, of emotional alterations or changes in character noticeable after the acute stages of encephalitis have passed, in many instances after recovery seemed otherwise to have been reached. These, so to speak, emotional residuals appear in varied form: in some cases the change is in the direction of a depressive affect, in others in the direction of an emotional elevation or irascibility, in still others explosive reactions, stubbornness, apathy, etc., are reported. The question has arisen, therefore, in many cases as to whether or not a permanent damage has occurred in the emotional sphere.

Motor Phenomena. From what we have learned regarding the sleep disturbance and the affectivity during the lethargy of encephalitis, we believe that the psychic torpor and emotional apathy are the most important mental factors in producing the stupor, while the rigidity and certain other muscular symptoms, when they occur during the stupor, are

the expression of a motor phenomenon of the sort seen in paralysis agitans. The tendency to hold given positions (catalepsy) seems to be most often associated with Parkinsonian symptoms, especially rigidity. We have not observed any symptoms of catatonic negativism in encephalitis cases, although it is well known that negativistic phenomena may occur in toxic-infectious disorders and in emotional settings other than dementia praecox. We have not seen spring-like resistance, release of an opposite impulse, fantastic postures, clenched fists, "schnauzkrampf," or cyanosis of the extremities. On the other hand, mutism, drooling of saliva, holding of urine, wetting and soiling the bed occur in the stupor of encephalitis and may be mistaken for negativistic reactions. To us it has appeared more plausible to bring them into relation with the psychomotor inertia and emotional apathy, a view which is supported by the patients' explanations obtained after emergence from the period of inactivity or stupor. The use of the term "catatonia" in describing motor or muscular phenomena of encephalitis seems to us to be misleading.

Psychotic Trends and General Mental Content. Ideas of a specific type are, of course, not to be expected in encephalitis any more than in other organic-infectious mental disorders. One has only to recall the multiplicity of delusional ideas encountered in syphilitic encephalitis or paresis, where such a great diversity of clinical pictures arises with brain changes of a very definite and specific character. Transient delusions or fixed ideas, independent of the delirium, do occur, but in general we may say that definitely formulated and persistent delusional trends are infrequent in the course of an encephalitis. Our series includes two fairly clear schizophrenic reactions one of which had begun prior to the encephalitis.

Mental Grasp, Orientation and Memory. Observers usually say that when patients can be aroused from lethargy or even stupor, that they are often remarkably clear as to their environment, etc. The degree of clearness can, however, vary a great deal even within a short space of time. A patient in a

lethargic or stuporous state may sink at any time to a lower level of consciousness, mutter and show "delirious dips" for a short or longer period. We have found on closer examination of awakened patients that although they may be generally clear as to the environment and recognize those about them, there are nevertheless evidences of interference with the mental processes and difficulty in grasp of more complicated things. This we interpret as a mental tension defect, such as occurs in organic reactions generally. We have found in our cases very little evidences that any severe or lasting impairment of orientation or memory follows the acute stages of the disease. The absence of any intellectual deterioration or dementia is especially noteworthy.

Briefly Put, the Conclusions Which we Are Inclined to Draw From our Study Are as Follows: The psychic disturbances of epidemic encephalitis present the general characteristics of an acute organic type of mental reaction corresponding more precisely to the group of toxic-infectious psychoses.

In the acute stages of the disease, pathological sleep, delirium and various mood alterations are the most striking mental disturbances, although other clinical pictures may be encountered, as the Korsakoff syndrome, or more complex mental disorders in which various affective and trend reactions add special features to the psychotic disturbance.

Although the mental disturbance is essentially of the acute organic type, this tends to recede as the early stages of the disease are passed; no marked mental reduction, intellectual impairment or dementia has so far occurred in any of our cases. On the other hand, we have found a great deal of evidence of persisting emotional alterations. In the majority of cases which have left the hospitals this emotional alteration constitutes practically the only evidence of a lack of mental recovery.

We are inclined to think that there is a special tendency for the emotional mechanisms to be directly or indirectly disturbed in encephalitis. As to the permanence of this alteration or damage, we cannot as yet give a definite

opinion. Whether or not these cases will later on show evidences of an (organic) mental deterioration is a question which we must also leave open for future determination.

The following questions submitted to Drs. Kirby and Davis before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask Dr. Kirby, who has no doubt had great experience in all forms of pathological drowsiness and stupor, whether there was something about the stupor of the epidemic encephalitis cases that struck him as rather different from the average case as one sees it? In other words, is there not something peculiar in the fact that a person, who appears to be in as deep a stupor as the average lethargic encephalitis case, is yet able to respond with considerable force, almost immediately to a question put him? Isn't that something that differentiates the stupor or the lethargy of these cases from the lethargy as observed in other forms of mental disease?

DR. KIRBY: I think in a considerable number of cases that is very striking and probably is not duplicated in other organic reactions. On the other hand, the ability to show mental clearness varies a great deal. Some cases one cannot arouse, and whether or not it is simply a question of degree or intensity, is something which perhaps one ought to take into consideration.

DR. SACHS: May I ask one more question? If Dr. Kirby were asked to speak of the most striking psychotic after-effect of epidemic encephalitis, would he perhaps allow that the persistent depression was as characteristic as any other, or is there any other psychotic state that he would mention?

DR. KIRBY: There is an emotional residual which I have referred to and which we think is one of the most significant after-effects of the disease, and in a great majority of cases I think that change is in the direction of a depressive effect, a distinct depression which sometimes may be hard to differentiate from an apathy unless one examines the patient carefully. I have been rather struck by the absence of any special feeling of sadness in this depression, and in that way it seems rather to differentiate from the more typical depressing conditions. The patients, although depressed, seem rather free from any special sadness or hopelessness regarding their future.

We have had some very interesting cases. Boys have shown a very marked change of character. After the disease, they have become emotionally unstable, very pugnacious, irascible, and quite a problem in the family. One patient is so disturbed that he is remaining in the hospital. In fact, it is rather significant—after a period of several months he has had a convulsion, which, of course, would indicate what I would call an organic foundation.

DR. SACHS: One more question. Have you seen any case, Dr. Kirby, in which a more or less chronic psychosis has been influenced to the good by the appearance of any epidemic encephalitis?

DR. KIRBY: No, I have not seen any.

DR. TAYLOR: Dr. Mulhouse offers the following question: Is the emotional residuum any different from that seen after influenza?

DR. KIRBY: The depressive tendency is very much like that which follows in influenza. I haven't seen after influenza these peculiar elevating mood reactions persisting for such a long time.

DR. TAYLOR: Apropos of Dr. Sachs' first question regarding the nature of the lethargy—whether it is analogous to, or a degree of, normal sleep,—did the patients have any recollection of the events during the lethargy?

DR. KIRBY: That is an interesting point. The patients remember a great deal of what they thought about during the lethargy, and if they had any delirium they remember the content of the delirium, but they don't remember where they were or their movements or any external events. That in a way is rather different from the psychogenic delirium where patients very often forget entirely their delirious trends.

DR. TAYLOR: Would that not also separate it from a degree of normal sleep and make it more or less a specific type?

DR. KIRBY: It might unless we thought of the normal dream as being constructed somewhat like a delirious experience.

DR. BARKER: Has Dr. Kirby found that encephalitis is more common in persons with an alcoholic history?

DR. KIRBY: We had only one in our series of 18 cases in which there was an alcoholic history. We haven't noticed that.

DR. BARKER: Has there been any difficulty in institutions for mental diseases in recognizing encephalitis in outspoken psychosis like dementia praecox?

DR. KIRBY: I think our experience has been that there have been

cases passing through the institutions that were not recognized until they came to autopsy. On the other hand, in the New York State Hospital, it might be rather interesting to report, that among 6,500 patients admitted during the hospital year there were 20 cases in which the diagnosis was made of encephalitis, probably not all definitely confirmed. So that the number of cases with severe psychotic manifestations arriving in the state hospitals seems to be relatively small.

DR. BARKER: Dr. Thomas in Baltimore has noticed a number of children who have had a persistent mental reduction after the attack. Has that been common here?

DR. KIRBY: We have had only two children in the series, and in both of them their mental after-effects were decidedly of an exaggerated emotional type—hypomanic tendency. We have tried to make very careful examinations of some severe psychotic patients that have been several months in a hospital to see whether or not there was any mental reduction in the sense of a deterioration of the intellectual faculties. We found that when a patient's attention and cooperation could be obtained he did remarkably well on all the thinking and intellectual tests. It was very striking. One man in a very marked state of indifference could retain and could do mental operations in quite an unusual way, showing that he was able to bring out emotional actions. At times one can also bring a patient to a higher life of intellectual activity by a stimulant.

DR. BARKER: In men past middle life we have had a few cases, thought by neurologists and psychiatrists to be either cerebral atherosclerosis or dementia paralytica, which afterwards turned out to be encephalitis. Has that been frequent in your experience?

DR. KIRBY: Several of our cases were considered in the beginning to be paresis. I mean on initial review. We haven't had any atherosclerotic complications in our cases.

DR. HUNT: I would like to ask if these psychotic types had associated with them other paralytic symptoms? Were those severe or were any of them of pure psychotic types indicating perhaps only cortical involvement, and have there been any autopsies in the psychotic types?

DR. KIRBY: We have not seen any very marked paralytic symptoms. We have seen some. One patient had a peculiar alteration of speech which disappeared. Our autopsy experience has not

been very extensive. We have had about 5 cases sent for examination. The complete working up of that material has not been accomplished yet. I do not think I would be prepared to say very much about the findings now.

DR. HUNT: The point I wanted to bring out was whether any of your cases in the earlier period were regarded as a spinal type or radicular type or cerebellar type or basal ganglia type or cranial nerve paralysis?

DR. KIRBY: We had a fairly representative group from the physical side. I did not say anything about that in the summary, but I think I have the facts of that here in my paper.

DR. TIMME: May I ask if any metabolic or biochemical studies have been made on your cases?

DR. KIRBY: None have been made.

DR. TIMME: Have observations been made as to any of these points regarding the rapidly changing clinical pictures such as those you have mentioned from stupor to activity? Are any observations made on the patients in those two rapidly changing states?

DR. KIRBY: The question of the variability of the patient as to clearness, we have gone into, and the question of the transitory delirious types or delirious manifestations we have tried to get the records of, and we have been impressed by the abrupt changes, not only the emotional reactions but the level of consciousness which these patients show. On one occasion a patient may be quite able to give good information; on another occasion he may appear decidedly less capable, more confused.

DR. TIMME: Have you made any observations, not particularly in your records, but will your memory serve you to let us know the changes perhaps in blood-pressure or pulse rate, showing changes on a level not only psychic but also vegetative in your experience?

DR. KIRBY: I am afraid we have not very many observations that we could use in that connection. The routine blood-pressure was taken in a good many of the cases; but, as regards the question of fluctuations, I doubt if our data would be sufficient to allow me to answer.

DR. ARONSON: I would like to ask Dr. Kirby whether he has observed hypersomnia in cases of encephalitis lethargica in which the amount or degree of sleep suggested to him a relation to possible pituitary involvement, congestive or perhaps inflammatory? Somnolence has been found in relation to some types of

pituitary affection, and on the other hand, many cases of epidemic encephalitis have shown considerable acromegalic disturbance either in the facies or in the extremities. Have you any memory of these conditions?

DR. KIRBY: I fear not. There are various theories regarding the lethargy and sleep; one has to take into consideration the activity of the pituitary, etc., but we really haven't any observations of any marked change in the general physical symptoms indicating that the pituitary has been involved.

DR. BARKER: Marie published a paper specially on the pituitary histological changes, and his conclusion was that they were noticeably absent—less than would have been expected.

AN ANALYSIS OF THE PSYCHOTIC MANIFESTATIONS OF 23 CASES OF EPIDEMIC ENCEPHALITIS, WHICH WERE ADMITTED TO THE PHIPPS PSYCHIATRIC CLINIC FROM THE SPRING OF 1919 TO THE SUMMER OF 1920 (LESLIE B. HOHMAN). Eight symptom complexes were observed and are presented in the order of their diagnostic importance.

1. *Great Push of Talk Without Distortion of the Stream of Talk and Without Mood Alteration.* This symptom was first called to our attention as a residual by Case 14. When given the slightest opportunity, the patient poured forth a minute, detailed description of all of his thinking and feeling. At first his talk was concerned with the material of his delirium and later with the discussion of the disease, its symptomatology, treatment, etc. The only possible way of stopping his talking was to keep everyone out of earshot. After four months of the disease, this was the only symptom persisting. In Case 10, this was the only abnormality observed which gave any clue to the diagnosis. The second patient was quite clear but seemed unable to control the incessant flow of words. The manic type of association—flight of ideas, distractibility, etc.—has not been present, nor does the mood show alterations to account for the talking. The patients are distractible and it is difficult to break in on the stream of utterance and divert the topic of conversation to other channels. Increase of general activity has been absent. One feels as if

all inhibitions to silence were off; the flood-gates are down and some force seems to drive from behind. In our cases this symptom was present in 8 cases.

2. *Euphoria, Jocularity, and Feeling of Well-being.* This has been one of the most striking symptoms. Thirteen of our cases (1, 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 14, and 23) have shown this at one time or another during the course of the disease. This sense of well-being reminds one in some respects of the euphoria of the paretic, but the cheerfulness does not seem as empty and vacuous as that of the paretic.

3. *Alertness and mental clearness*, when the patient is once aroused in spite of the presence of stupor and somnolence.

When the disease first began to be seen, one was amazed when the patient dropped off to sleep during examination.

The clearness and alertness which the patients show immediately upon being aroused from their sleep is equally surprising. One would not expect as much wide-awakeness from a normal person aroused from sleep. It is probably true that the somnolence appears deeper than it really is because of the ptosis that so frequently exists.

4. *Delirium.* Delirium has been noted in 14 and possibly 15 of our cases. This term is used to describe any psychosis in which there is a dreamy state with clouding of consciousness, disorientation and a type of association in which drifting and groping are present. Following Hoch's classification of the deliria as organic and psychogenic, it was found that practically all of our cases fell into the organic group. The content of the delirious utterances concerned itself almost exclusively with topics which did not involve the personality of the patient in any of the instinctive realms. Occupation delirium was the most common type seen (Cases 1, 5, 6, 9, 13, 14, 19, 21), and this has been the rule in cases reported by other observers. In 3 of our cases (14, 15, 16) the delirium was accompanied by an affect of fear.

5. *Stupor States.* Frequently at the onset of the disease stupor states have been observed (5 of our cases). These stupor reactions have been mistaken for schizophrenic

stupors. However, it seems to us that the schizophrenic makes use of voluntary motor mechanisms and there is rarely observed the incoordinate tremor and tonic rigidity seen in the encephalitic stupor. In addition, the stupor does not arise in a schizophrenic setting. Again, the clearness of the catatonic stupor is absent.

6. *Behavior Oddities.* Impulsive or unusual acts totally out of keeping with the rest of the activity of the patient have been seen in 7 cases. This is as one would have expected in any psychosis having an organic basis. The impulsiveness of the paretic and arteriosclerotic groups is well known. Frequently, however, the oddity has been so unusual, unmotivated, and in some cases so silly that it has impressed the observer as being significant. For instance; Case 3 tried to commit suicide by hanging herself with a shoe string without any real desire to kill herself. Case 1 got out of bed suddenly, dashed down the long corridor, and when brought back said, "Why do I do things like this?" She was not frightened and the act seemed totally unmotivated. Case 2 bathed practically the entire day, wrote an extraordinary number of letters, and took huge doses of cathartics. Case 11 showed a very odd, stilted talk, using words in a high-flown, silly manner. In the midst of a formal conversation he would swear violent oaths without any anger. Case 13, although he had been in bed for weeks and was very somnolent most of the time, would get up suddenly, go to his wardrobe, pack his suit-case and announce that he was leaving for home. Case 15 attempted suicide on two occasions by actually walking out of the third story window. Case 16 had temper tantrums without precipitating causes and totally out of keeping with her former disposition. Case 17 would get out of bed and wander about looking for medicine. She was not delirious and knew well that she was in isolation.

7. *Depression Has Been Observed in Seven Cases.* In our Cases 6, 7, 21, it was a transitory symptom but was pronounced and prolonged, in fact dominating the clinical picture in Cases 15, 16, 18 and 20. Suicidal attempts have

been frequent and at least 2 cases were brought to the hospital for just this reason. In Case 15 there was the formal alteration of thinking and activity which characterizes the manic depressive, i. e., slowness of thinking and talking, morning-evening variation, etc. Case 17 showed a deal of puzzling bewilderment and fear as well as depression. In Cases 18 and 20 there was no slowing.

8. *Emotional Instability and irritability* have been very frequent incidents of the disease, especially the latter. Tantrums and anger outbursts have occurred without obvious cause. The lability and overflow of emotional response has suggested a pseudobulbar syndrome in Cases 1, 5, 8, 9.

9. *Memory Defect.* It was rather surprising to find no little evidence of real, permanent memory defects in our cases, since we are dealing with a disease in which there is demonstrable alteration of brain substance. In all four cases (8, 11, 13, 22) in which memory defect was demonstrated (of course the acute deliria are excluded) the prime difficulty was in recent and immediate (retention) memory. Case 8 in addition confabulated freely. With an alcoholic history this case might easily have passed as a Korsakoff syndrome. All forms of our cases showed a preliminary period of delirium with recent memory and retention difficulty.

In our cases, four main reaction types can be made out:

1. Depressive.
2. Psychoneurotic-like.
3. Delirious.
4. Organic.

The same interesting inquiry arises here as in the consideration of psychoses due to the parenchymatous lues. Why should one patient react with a manic excitement, another with a depressive reaction, and a third with a paranoid or a classical picture of general paralysis?

Unfortunately the post-mortem findings offer us no explanation. We are of the opinion that with diffuse organic change the personality and constitution of the patient is

apt to run amuck at its points of greatest vulnerability. That is, a personality or constitution which is able to maintain an adequate adjustment with the proper repression or sublimation of unsocial trends or strong instinctive drives breaks along these lines when the automaticity of adjustment is interfered with. Some of our cases bear out this notion admirably.

1. *Depression Reaction Type.* In 7 cases this type of reaction was observed, but in only 2 cases were there the formal thinking and activity alterations, i. e., slowness of the manic-depressive reactions. The other cases resembled the reactive and psychoneurotic depressions. The depression has usually been admixed with short phases of delirium.

2. *Psychoneurotic-like Reaction Type.* Several of our cases were admitted to hospital with the diagnosis of hysteria or functional disorder. The clinical picture in several cases was gastric, abdominal, and thoracic hypochondriasis. Careful physical and laboratory examinations revealed no cause for these complaints. Suggestive therapy often relieved symptoms, but we were inclined to regard them as probably due to actual if slight organically determined functional deviations. Our attitude has been to treat them as psychoneurotic because these features offered more chance for therapeutic aid than did organic alteration.

3. *The delirious reaction type* has already been discussed under symptomatology.

4. *The organic reactions* are essentially the outcome of the protracted delirious reactions with permanent reduction due to permanent damage. They have been characterized by the presence of memory defects (in the main for recent events and for retention), with a tendency to confabulate, and good humor and sense of well-being. Probably the impulsive activity noted above is also best explained in terms of the organic alteration.

The following questions submitted to Dr. Hohman before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: Your summary I think is excellent. The only thing that would be surprising, I think, to some of us, is the number of cases of euphoria that have been reported. Outside of institutions I doubt whether many such cases have been observed. Was that a euphoria that would be as distinct, for instance, as the euphoria of a general paresis?

DR. HOHMAN: I think rather more good humor and cheerfulness.

DR. SACHS: It was not as distinct as that of general paresis?

DR. HOHMAN: It was less vacuous but more real good humor and cheerfulness. It stood between the vacuous and the empty euphoria and hypomanic good humor of the hypomanic state. The patients felt fine, like new-born babes and things of that sort.

DR. BARKER: Have any of the organic type had the Argyll-Robertson pupil?

DR. HOHMAN: I think one did but I am not quite sure.

DR. SACHS: Here is a question that has been put: Have spinal punctures been tried in these cases, especially in those that were hyperactively delirious and were suffering from insomnia?

DR. HOHMAN: Yes, repeated lumbar punctures have been done. There was one case in particular in which there was a reversal of the sleep curve and in addition this great push of talk. There have been repeated lumbar punctures and as far as we can observe nothing was accomplished thereby.

DR. TIMME: You mentioned as some of the symptoms, on a vegetative level, thoracic and abdominal hypochondriasis?

DR. HOHMAN: A great deal of abdominal pain and cramps and pains in the chest, things that would have suggested girdle pains, and complaint of things that might have passed as pleural pain. All of the physical examinations and careful sensory examination revealed nothing. Also endocrine studies were made and nothing could be made out of them.

DR. LADD: You say that you place the deliria in the organic class differing from dementia praecox of psychogenic origin and state that this was done because of the hypertonicity not being present in the psychogenic mechanism. How do you consider the tonicities in catatonic types of dementia praecox with psychogenic deliria?

DR. HOHMAN: I did not say that. I put the deliria as organic and psychogenic. I classify as organic the things that have ordinarily occurred in the toxic deliria, whereas the psychogenic delirium is the hysterical delirium which makes use of various disturbances

—as those things which arise in hysterical or other delirious states in which psychogenic mechanisms are used.

DR. SACHS: May I ask whether in Baltimore you observed any improvement in the chronic forms in any case after an occurrence of this form?

DR. HOHMAN: Of the 4 cases which occurred in the organic group, 2 are dead and the other 2 are still in the same condition. Unfortunately, both those deaths occurred outside of the hospital and we could not make an autopsy.

DR. HUNT: Did all these cases contain evidence of some organic disease of the brain, some paralytic infection in the cranial nerves or elsewhere in the early stage?

DR. HOHMAN: In one case, the second case I spoke of, there was this great push of talk for the first week—nothing except this incessant flow of talk was observed. Later he developed a facial weakness, etc. We have insisted upon the finding of two abnormal things in the cerebral spinal fluid to make our diagnosis. That is arbitrary, but we did not include a lot of things which might have been regarded as encephalitis unless they had actual spinal alterations, cell count change, change above ten, or alteration in the colloidal gold reaction, etc. Unfortunately we did not do sugar studies.

CONCLUSIONS OF THE COMMISSION

It is the opinion of the Commission that the views postulated in this section by Drs. Kirby and Davis and by Dr. Hohman offer the correct interpretation of the psychotic manifestations of epidemic encephalitis, namely, that the mental symptoms found are those which are in the main consistent with those which occur in organic brain disease, and that they are to be interpreted as directly attributable to the disease process.

The above investigators have brought out facts of particular interest in the symptomatology of the disease, especially in respect to emotional disorders of various kinds, sleep disturbances and certain peculiarities of conduct. They have likewise emphasized that the symptomatology is quite unusual at times and differs from that which is seen in other organic brain diseases. All investigators have

expressed the opinion that these symptoms are part of an acute organic psychosis and are not to be confused with other psychoses. Further clinical observations of the psychotic manifestations associated with epidemic encephalitis are necessary before conclusions are warranted as to the ultimate outcome of these mental types. The observations have not been over a period long enough or of a sufficient number of cases to warrant a prognosis. It will be of interest to know whether these cases eventually recover, whether they remain permanently disabled, particularly in emotional spheres, or whether they will deteriorate. In view of the nature of the disease, the possibility of recurrences in the psychotic states is of interest. The similarity of some psychotic cases of epidemic encephalitis to catatonic forms of dementia præcox in superficial appearance is of considerable interest.

The Commission wishes to refer briefly at this time to the observations of Drs. Morris Grossman and Junius W. Stephenson on some unusual conduct disorders occurring in children after attacks of epidemic encephalitis. Likewise, other contributors to the volume, as well as those in this chapter, have made mention of neurasthenic and psychasthenic sequelæ. The changes in character and disposition of children after having suffered from this disease are of unusual interest; and the various tics and habit spasms which the above investigators have observed after the disease in children are likewise of great interest. The Commission therefore feels that the mental manifestations associated with lethargic encephalitis, as reported by the above observers, may be divided into three large groups: the frank psychoses, the psychoneuroses, and the changes in temperament and conduct disorders. Continued study of the origin, course and outcome of these particular mental symptoms in epidemic encephalitis will not only throw light upon the disease itself but should also furnish insight into the characteristics of psychoses, psychoneuroses and conduct disorders occurring under other circumstances.

CHAPTER V

DIAGNOSIS, COURSE AND PROGNOSIS; LATE RESULTS

THE opinion of the Commission on the topics embraced in this chapter is based upon the investigations, experiences and classifications of the following contributors: Dr. Lewellys F. Barker of Baltimore, who treated the subject of diagnostic criteria; Dr. William B. Cadwalader of Philadelphia, whose especial investigation was in the field of the differential diagnosis between epidemic encephalitis and anterior poliomyelitis; Dr. Morris Grossman of New York and Dr. Junius W. Stephenson of New York, on the prognosis in epidemic encephalitis; all of whom were especially designated by the Association to cover the special divisions included in this chapter.

DIAGNOSTIC CRITERIA IN EPIDEMIC ENCEPHALITIS (LEWELLYS F. BARKER). In no other condition, perhaps, is a general diagnostic survey, and especially a general neurological and psychiatric survey, more important for accurate diagnosis than in the epidemic encephalitis. When, however, the symptoms and signs that are recognizable by modern methods have been accumulated, and when the sites within the nervous system to which they point have been carefully determined, there is now in most cases but little difficulty in deciding upon a diagnosis of encephalitis if the disease is present.

In the United States, initial stages of various sorts have been described. When the onset was sudden, there was often severe pain in the head, fever and delirium, followed by a period of improvement for a few days, after which

apathy, somnolence and cerebral nerve paralyses of different sorts or Parkinson-like syndromes developed. When the onset was more insidious, the initial symptoms often consisted of diplopia and slight mental confusion, or, in some cases, of neuralgias or of pareses in the domain of one or more of the cerebral nerves; and these patients, too, often showed improvement for a few days only to become somnolent later. Not infrequently there was marked restlessness at night with insomnia before a stage of somnolence was reached. Of the abnormal mental symptoms exhibited by encephalitic patients, somnolence or pathological drowsiness is by far the most important as a diagnostic criterion. The deliria that occur in encephalitis are less characteristic than the somnolence.

It is useful from the standpoint of diagnostic criteria to adopt, for the present, the following dominant clinical types.

1. The somnolent-ophthalmoplegic type (febrile or afebrile).

2. The paralytic (akinetik or hypokinetic) type.

3. The amyostatic type (Parkinson-like and cataleptic syndromes).

4. The hyperkinetic type (myoclonic forms, choreatic forms, epileptic forms).

5. The psychotic type (delirious forms, maniacal forms, depressive forms).

6. The hyperalgetic type (painful forms).

7. The tabetic type (Argyll-Robertson pupils with loss of deep reflexes and, sometimes, with lancinating pains).

8. The ataxic type.

9. The abortive type (formes frustes; imperfect, rudimentary, and ambulatory forms).

10. The aberrant type (intestinal forms, cutaneous forms, vagal forms, etc.).

The occurrence of any one of these syndromes at a time when encephalitis is epidemic, especially when it is associated with signs of infection (fever or leukocytosis), should make

one think of the possible existence of the disease we are considering.

The Criteria for Determining the Sites of the Lesions in Epidemic Encephalitis. Many of the syndromes above mentioned are now known to be due definitely to certain focal lesions within the nervous system.

The somnolent ophthalmoplegic syndrome points of course to the interbrain and the midbrain particularly.

The akinetic and hypokinetic syndromes (other than ophthalmoplegia) are usually easily localizable.

The amyostatic syndromes (including the Parkinson-like syndrome and cataleptic rigidity) are most interesting as localizing guides. (Injury to the corpus striatum.)

The several hyperkinetic syndromes may also be valued to a certain extent for localizing purposes.

The psychotic types doubtless depend upon diffuse toxic disturbances or multiple foci of infiltration in the telencephalon.

Multiple pains of neural or radicular distribution point to a multiple neuritis or radiculitis.

A fair degree of success could, from what has been said, be achieved in the construction of a classification based upon the different localities in the nervous system that are the sites of the toxic-infectious processes in encephalitis. The term *encephalitis* would include (1) all the inflammatory processes from the telencephalon to the mesencephalon inclusive (*telencephalitis*, *diencephalitis*, *mesencephalitis*), these together making up *cerebral encephalitis*, and, in addition, (2) all the inflammations of the rhombencephalon (pons and medulla oblongata), including *pontine encephalitis* and *bulbar myelitis*. Under the term *myelitis* would be included all the inflammations that occur in the spinal cord in this malady (*poliomyelitis anterior*, *poliomyelitis posterior*, *myelitis transverse*, and *myelitis funicularis*. Under *neuritis* could be included the inflammations that occur in the extra-central portions of the cerebral and spinal nerves (*radiculitis*, *peripheral neuritis*). Under *meningitis*, or rather *lepto-*

meningitis, would be included patchy inflammations of the soft meninges. Various combinations of these different local inflammations are met with in a single case. In some instances it would seem legitimate to speak even of a meningo-encephalo-myelo-neuritis.

Differential Diagnosis of Epidemic Encephalitis. The neurological and psychiatric data having been collected, the co-existence of symptoms and signs constituting one or more of the type syndromes having been recognized, and the consideration of the clinical findings for their localizatory significance having been completed, sufficient evidence is as a rule at hand to permit one to decide whether the patient under study is or is not suffering from epidemic encephalitis.

Caution is always advisable, however, before permitting one's self to arrive at a definite diagnostic conclusion. For epidemic encephalitis may mimic very closely any one of a whole series of neurological and psychiatric conditions of another nature; and the reverse is of course also true—these conditions may wear the guise of one or another form of epidemic encephalitis.

In the first outbreaks of epidemic encephalitis in Europe, "botulism," meningitis," and the "Heine-Medin disease" were the erroneous diagnoses most often made. In the Winnipeg epidemic (1919), cases that were diagnosed clinically as "cerebral hemorrhage," "uremia" and "tuberculous meningitis" were found at autopsy to have been cases of encephalitis (William Boyd).

Among the *infectious processes* with which epidemic encephalitis is likely to be confused, the following stand out prominently: (1) meningitis, (2) influenza and grippe infections, (3) the Heine-Medin disease and (4) multiple neuritis, especially the infectious form. Confusion may also occur, though less frequently, with (5) typhoid fever, (6) mumps, (7) infectious arthritis or myositis, (8) tetanus, or (9) hydrophobia. Here, too, should be considered the differentiation (10) from forms of encephalitis, myelitis or encephalomye-

litis other than those due to the specific virus that must be responsible for the present epidemic.

Among the *intoxications* which may closely resemble epidemic encephalitis with somnolence may be mentioned (1) uremia, (2) acidosis, (3) cholemia, (4) drug-intoxications (veronal poisoning, cocaine poisoning, alcoholic intoxication, etc.), and (5) botulism.

The vascular lesions most likely to give rise to states that may be confused with epidemic encephalitis are: (1) cerebral hemorrhage; (2) cerebral thrombosis; (3) cerebral embolism; (4) sinus thrombosis, and (5) cerebral atherosclerosis.

Cerebrospinal lues, dementia paralytica and tabes dorsalis are sometimes believed to exist when the patient's state is really due to epidemic encephalitis.

Epidemic encephalitis may occasionally give rise to clinical pictures that make one think of cerebral tumor, cerebellar tumor, pontile tumor, or tumor of the cerebello-pontile angle.

Myoclonias. During the past two years myoclonic forms of epidemic encephalitis have been frequently observed.

Chorea. Many choreiform manifestations have been met with since the hyperkinetic forms of epidemic encephalitis have been prevalent.

Parkinson's Disease. Parkinson-like syndromes, especially paralysis agitans sine agitatione with pyramidal tract symptoms have been frequently met with among the encephalitic cases in all countries in which the epidemic disease has been fully described. The acute development of this amyostatic syndrome (rigidity, characteristic attitudes, facial mask, and poverty of movement with or without tremor) and the surprising disappearance of the phenomena, in many instances in the course of a few weeks, have been striking features of this type of encephalitis.

Cataleptic or Catatonic States. In the first English epidemic, many of the cases of encephalitis were described under the name of "epidemic stupor" and in other countries

cataleptic states, catatonic states and waxy flexibility have been described as a part of the symptomatology of many cases of epidemic encephalitis.

Myasthenia Gravis. Several of the patients suffering from encephalitis in this epidemic have at first been thought to be suffering from myasthenia gravis, owing to certain manifestations (profound asthenia; general muscular weakness; and, especially, weakness of muscles innervated by the motor cerebral nerves, exhibited as ptosis, facial paralysis, dysmimesis, dysarthria and dysphagia).

Progressive Central Muscular Atrophy. Either the spinal or the bulbar form of progressive (central) muscular atrophy may sometimes be simulated by the more subacute forms of epidemic encephalitis.

Hysteria and Neurasthenia. Some of the more obscure forms of epidemic encephalitis have been erroneously supposed to be cases of hysteria or of neurasthenia. The pathological drowsiness of encephalitis may be confused with hysterical twilight states or hysterical narcolepsy. The residual neuralgias, the restlessness, the insomnia and the disturbed mentality of the convalescent encephalitic may be ascribed to neurasthenia or to psychasthenia.

CONCLUSIONS

On account of the toxic component and of the inflammatory infiltrative component of the disease-process, both general and widely disseminated focal manifestations of involvement of the central and peripheral nervous systems may occur in encephalitis and give rise to the most diverse disturbances of motility, of sensation, of coordination, of the reflexes and of the psyche.

Despite the enormous number of clinical forms met with in epidemic encephalitis, there is a marked tendency to the repetition of certain characteristic forms or types, of which the somnolent-ophthalmoplegic, the paralytic, the amyostatic and the hyperkinetic are the commonest.

When the disease is epidemic it can usually, in outspoken cases at least, despite the clinical diversity, be easily recognized, though in abortive, imperfect, rudimentary and aberrant cases, great difficulties in diagnosis may be experienced and doubtless many cases remain entirely unrecognized.

The occurrence in a patient of (a) pathological drowsiness (lethargy), (b) cerebral nerve paralysis (especially ophthalmoplegia), (c) an acutely developing Parkinsonian syndrome, (d) a cataleptic or a catatonic state, (e) a myoclonia, (f) a chorea, (g) pupillary disturbances, (h) violent neuralgia, (i) a poliomyelitic syndrome, (j) a peculiar delirium, (k) a psychotic state, or (l) signs of meningeal irritation in times when encephalitis is epidemic should make one think of the possible existence of the disease.

Though epidemic encephalitis may simulate any one of a large number of neurological and psychiatric syndromes of entirely different origin, the mode of onset, the course, and the results of carefully conducted neurological and psychiatric examinations (including an examination of the cerebrospinal fluid) will usually yield the diagnostic criteria that suffice for its recognition and differentiation.

The following questions submitted to Dr. Barker before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TIMME: Dr. Bailey has sent in a list of four or five questions which I will ask the secretary to read for the bringing out of some of the prominent points.

DR. KENNEDY: What are the characteristics of amnesia and memory disturbances?

DR. BARKER: In the cases that I have seen there is frequently loss of memory for the events that occurred at the time of the onset of the drowsiness. I remember one patient made a long automobile trip and was awake part of the time and asleep part of the time, and lost all memory afterward of what had occurred during that trip. A second feature has been the Korsakoff type

of memory disturbance where there was disorientation for time, place and persons, and pseudo-reminiscences, confabulation, and the third type of memory disturbance was more like that seen in dementia paralytica, or in some of the forms of cerebral atherosclerosis with especially loss of memory for recent events, diminution of the recording faculty, with fair preservation of the older memories.

DR. KENNEDY: What is the average duration of such prodromata as headache, sore throat, general weakness, etc., before definite symptoms of the disease become present?

DR. BARKER: In my own cases it has been hard to determine that. I have seen them as a rule in the latter stages, and it was hard to get an accurate history, but it seems to vary a great deal. There were some in which the prodromata lasted only a short time; others in which there had been complaints over quite a long period, and that seems to be in accord with the reports in the bibliography.

DR. KENNEDY: Does the reaction to the infection show any variations in different races or in predisposed individuals? And that raises another question, Has any predisposition been demonstrated?

DR. BARKER: Reactions are so different in the different epidemics; I think that those differences are more outstanding than racial differences. If one studies, for instance, an account of the two epidemics in Austria and the recent epidemic in Italy, and the epidemics in Germany, in France and in this country, one will see that there are very great differences in the clinical picture in successive epidemics in the same country, and the same kinds of pictures have come out in all the countries if one studies the bibliography carefully. As to predisposition, the literature is pervaded with histories of influenza before the attack, although large numbers of the cases have no preceding history of influenza, and there are many who think that the so-called influenza was really this disease at the beginning rather than an ordinary influenza. The only other predisposing factor that I have seen is alcoholism. I have seen several alcoholic cases that developed encephalitis, but they are not specially numerous considering the total number of cases seen. I think I was impressed by that because I was on the lookout for alcoholics especially.

DR. KENNEDY: What percentage of cases run their course without mental symptoms?

DR. BARKER: It would depend on how you define a mental

symptom. If you include pain and drowsiness as mental symptoms, I think the percentage would be very small, but if you mean without deliriums or psychotic states, I think there is a large percentage. That is an impression without any definite figures.

DR. KENNEDY: The last question—What post-mortem verifications are there for various localized symptoms mentioned?

DR. BARKER: I have none of my own; I have no autopsy. There have been some at the hospital. In the literature there is a growing body of material with confirmation of the present existent knowledge upon the relation of clinical syndromes to sites of lesions. I think almost all that we know and say about the localization of lesions at present is based upon our general knowledge of neurological localizing diagnosis, and where a confirmation has been possible it has been made. There has been a good deal of confirmation especially of the bulbar and other lesions, and in the poliomyelitic syndromes they have been verified at autopsy in a good many cases.

DR. PRINCE: May not acute idiopathic internal hydrocephalus (Quincke) simulate the ophthalmoplegic type, and how would you differentiate this condition?

DR. BARKER: Yes, I think it could simulate it. As I recall, it is a febrile Quincke. It might be very difficult to differentiate. I think you would be much more likely to suspect encephalitis than that condition on account of its rarity in times of epidemic.

DR. PRINCE: I note that it has not been mentioned at all in the discussion, and I think it has the same ophthalmoplegia as the headache, etc., but the symptoms are variable. I have seen three cases. It seems to me it might be very difficult at times to differentiate.

DR. BARKER: Would lumbar puncture show any differences? If there was an increased cell count, positive globulin, that would favor encephalitis, but half the cases of encephalitis have a negative fluid. Is it quite certain that the Quincke syndrome is not an encephalitis? (Laughter)

DR. PRINCE: Merely in the autopsies there have been found no inflammatory conditions at all at the base of the brain or any part of the brain, in fact; even of the choroid plexus, etc., no inflammatory conditions were found. I do not know of any examination that has been made of recent years, but microscopically nothing has been found.

DR. PATRICK: I have a question by Dr. Davis: If in general paresis there is not a toxemia but a syndrome based on anatomical localization of spirochete, have we any reason to think epidemic encephalitis not a toxemia but instead entirely dependent on anatomical localized growths of the encephalitis virus?

DR. BARKER: My answer to that would be entirely speculative. In the first place, I am not quite convinced that the whole picture of dementia paralytica is devoid of intoxicating element. We know there is an inflammatory element, due to localization, but there may also be a chronic intoxication. There is a good deal of evidence, I think, especially since von Economo's last paper, of a marked toxic element at the beginning of this disease of epidemic encephalitis which is apparently responsible for the diffused processes in the very early stage of the disease, and the inflammatory infiltrative changes which occur apparently only later. It does seem as though epidemic encephalitis had both a toxic component as well as an inflammatory infiltrative component, and the evidence is in the internal organs. Von Economo has had made in a laboratory in Vienna a number of metabolical studies, blood chemistry and urinal function studies, very suggestive of a toxic process as well as of an inflammatory infiltrative process.

DR. TAYLOR: You spoke of the cataleptic type; to what extent have you observed that cataleptic manifestation, or how cataleptic was it?

DR. BARKER: I have used the term cataleptic as synonymous with catatonic rigidity. I have seen two cases that would be looked upon easily as catatonic stupor, where the patient lay like an image on the bed—immobile, apathetic, making no movement, hardly answering questions, not taking food, not speaking, marked poverty of movement, very much like what is ordinarily described as a catatonic state, and I think that in the English epidemic a large number of the cases described as epidemic stupor seemed to have been of that type. Nonne has described them in the Hamburg epidemic as quite common—this image-like, rigid, immobile type, without quite the Parkinsonian mask but with almost waxy flexibility.

DR. TAYLOR: I should like to know whether this cataleptic type was to the extent of the patient preserving any position which one would give him.

DR. BARKER: Some of them have definitely held a passive position given to the limbs.

DR. BROWN: Have you seen prolonged neurasthenic or psychasthenic states following lethargic encephalitis?

DR. BARKER: Yes.

DR. FREEMAN: Has paralysis of associated lateral movements of the eyeballs been observed in epidemic encephalitis?

DR. BARKER: Yes. It is not common, but it has been observed.

DR. DANA: Have you observed the phenomenon that Dr. Abrahamson speaks of—that all cases of this encephalitis were ushered in by some mucous membrane irritation? He speaks of that as being uniformly the case. It has been overlooked by most observers, but if observations are carefully made you will find that a patient has a pharyngeal irritation or nasal irritation, or oral or bronchial or intestinal, that precedes the disease.

DR. BARKER: I have seen relatively few cases at the very beginning myself. I had not been especially impressed with that point, though a history of nasal pharyngitis is not uncommon in the literature preceding cases, and there is one group of cases described as an aberrant form in which intestinal symptoms have been pronounced. I have seen one or two that developed intestinal symptoms during the course, but I have not been especially impressed with mucous membrane inflammations as an antecedent.

SPECIAL DISTINCTION BETWEEN EPIDEMIC ENCEPHALITIS AND POLIOMYELITIS (WILLIAM B. CADWALADER). In considering the relation between epidemic (lethargic) encephalitis and acute anterior poliomyelitis, much depends upon whether the subject is studied from the purely clinical aspect, or from exact comparisons made with post-mortem material. In each disease, however, careful examinations by both methods should be made before conclusions are drawn.

It is a firmly established fact that several types of exudative inflammations of the brain are infectious in character. It is not possible, however, from microscopic examinations of tissues alone, to separate with precision the alterations produced in the nervous system by each of the different known agents. True, certain individual cases have been recorded from time to time in which characteristic differences

seem to be present, but when these points are analyzed carefully, it can generally be shown that they are based chiefly upon the situation of the lesions, or are apparent variations caused by modifications in the intensity and duration of the disease. They cannot, therefore, be regarded as characteristically different tissue reactions corresponding strictly and precisely to various infectious agents.

This opinion has frequently been expressed by different authors, and especially in regard to the practical impossibility of separating the lesions of acute anterior poliomyelitis from those of epidemic (lethargic) encephalitis when examined under the microscope.

It is not surprising, therefore, that the clinical differentiation may also be quite impossible.

Like the onset of acute anterior poliomyelitis, that of epidemic (lethargic) encephalitis is an exceedingly irregular one. From the studies made during epidemics by Wickman and others we learn that an abortive type of poliomyelitis in which paralysis is absent is frequently encountered, and thus our present conception, that acute anterior poliomyelitis is an infectious systemic disease in which paralysis may or may not occur, has become established. The number of cases of acute anterior poliomyelitis in which paralysis is absent varies considerably in different epidemics, but most observers agree that the abortive types represent about 50 per cent of all cases of the disease.

Comparing the onset and development of epidemic (lethargic) encephalitis, almost all recent observations show that the condition is dependent upon a previous attack of influenza. Epidemic (lethargic) encephalitis is not, as a rule, a part of an attack of typical influenza, but it is a well-known fact that epidemic (lethargic) encephalitis may follow an attack of influenza. For this reason, premonitory symptoms, or those preceding the development of paralysis in epidemic (lethargic) encephalitis, may be the same as those of infection, or merely incidents in the convalescence from that disease. This stage of the disease, therefore, in which the

symptoms resemble those of a chronic influenzal infection, represents the general systemic phase, which is exactly analogous to the abortive or non-paralytic types of acute anterior poliomyelitis. It may, however, progress and become a specialized expression in the form of an affection of the central nervous system with paralysis. In this respect the diseases are closely similar, and it seems unnecessary to quote here the details of cases showing no paralysis. For present purposes it is quite sufficient to refer to the fact that the differentiation of non-paralytic cases of acute anterior poliomyelitis, and of non-paralytic cases in which influenzal infection of the nervous system is suspected, is dependent largely upon the knowledge of the occurrence of an epidemic of acute anterior poliomyelitis or the prevalence of influenza or of epidemic (lethargic) encephalitis in the community in which the cases are observed.

Considered topographically, there are certain well-recognized forms of acute anterior poliomyelitis in which the inflammatory process is well localized and reaches its greatest intensity in the cerebral peduncles, pons, or medulla oblongata, the spinal cord and cerebral hemispheres being unaffected. These are the cases that show the strongest resemblance to epidemic (lethargic) encephalitis. The weight of opinion, moreover, strongly favors the view that the polioencephalitis superior and inferior or the polioencephalomyelitis of Wernicke is true influenzal encephalitis, and merely modifications in type of the same disease.

Epidemic poliomyelitis is generally believed to occur during the hot weather, particularly in July and August. Most of the victims are children, and the lower motor neuron type of paralysis is that most frequently encountered in cases with paralysis. The onset is sudden. Epidemic (lethargic) encephalitis is believed to occur chiefly during the winter months, the majority of cases having been met in adults. Not rarely a greater number of cases are seen in which only the cranial nerves are affected, and there is prolonged lethargy, which is rare in acute anterior poliomye-

litis. While such tendencies are important, they are of no value in determining the nature of the disease in a given case.

Lethargy is not always present in cases of epidemic (lethargic) encephalitis; moreover, it occasionally occurs with acute anterior poliomyelitis. Lethargy in various degrees, stupor, or somnolence, frequently with delirium, may occur from intoxication in many different infectious processes, and while very common in epidemic (lethargic) encephalitis, it is not in itself characteristic of the disease.

The clinical manifestations exhibited by lesions in the mid-brain are most varied. Any extensive lesion in the bulb is almost invariably rapidly fatal, but the acute symptoms in both acute anterior poliomyelitis when it affects the bulb, as well as in epidemic (lethargic) encephalitis, may be severe. Nevertheless, they will often clear up, leaving a paralysis limited to one or more cranial nerves. In acute anterior poliomyelitis the seventh or facial nerve is said to be most frequently affected, whereas the third nerve is most often affected in epidemic (lethargic) encephalitis, and also in Wernicke's polioencephalitis. Diplopia is, therefore, an early sign. However, any of the cranial nerves, as well as the limbs, may be paralyzed in each of these diseases, from involvement of the pyramidal tracts from within the bulb. Neither the character of the paralysis of the individual cranial nerves nor combinations of types, such as unilateral, bilateral, or multiple or single, have any significance in determining the etiology. These phenomena merely furnish indications of the locality of the inflammation, and the direction and extent of its distribution.

Cases of so-called influenzal myelitis have been observed from time to time.

A somewhat rare manifestation of acute anterior poliomyelitis is a transverse lesion of the spinal cord, the patient exhibiting complete flaccid paralysis of both legs, loss of sphincter control, and absence of sensation up to the level of the lesion. The latter may remain complete or may clear up, leaving the patient with spastic paraplegia with in-

creased knee-jerk, defective control of the bladder, etc. It must be admitted that positive proof that such cases are caused by the virus of acute anterior poliomyelitis is lacking, yet Batten (*Brain*, 1916, xxxix, 1 and 2) observed such cases during an epidemic of acute anterior poliomyelitis. B. Sachs (*J. Nerv. & Ment. Dis.*, 1912, xxxix, p. 757) recorded a case of acute anterior poliomyelitis in a girl aged eighteen, with sudden onset of complete flaccid paralysis and loss of sensation up to the xiphoid cartilage, with complete recovery in two months. The cerebrospinal fluid showed a high lymphocytic count.

Netter and Levaditi (*Bull. et mém. Soc. méd. d. hôp. de Par.*, 1914, Ser. 3, xxxvii, 570) reported 4 cases presenting symptoms of transverse myelitis which they attribute to the virus of acute anterior poliomyelitis. These authors were able to show that the blood of a patient who had recovered, possessed the property of neutralizing the virus of acute anterior poliomyelitis.

The writer recently observed a similar case in an adult, in whom there was a history of an attack of influenza one year prior to the onset, and a chronic cough and pharyngitis that had persisted until within a few months preceding the onset of the present condition.

In cases of epidemic (lethargic) encephalitis the spinal cord is not, as a rule, believed to be affected. In acute anterior poliomyelitis the spinal cord is involved much more frequently than other portions of the nervous system. At a meeting of the Philadelphia Neurological Society, held in November, 1920, Winckleman and Weisenburg reported a very important case of epidemic (lethargic) encephalitis which they had observed clinically and at post mortem, and had found the usual evidences of that disease in the basal ganglia, reaching the greatest intensity in the pons and medulla oblongata. They also found intense perivascular infiltration and edema limited to the gray matter of the cervical and upper thoracic portions of the spinal cord. These alterations were identical in character and in location

to those usually found in cases of acute anterior poliomyelitis, thus proving conclusively that in epidemic (lethargic) encephalitis the spinal cord may be affected.

A closely similar case is that reported by Harbitz (*Norsk. Mag. f. Lægevidensk.*, Kristiania, January, 1920.)

Local muscular atrophy is the one outstanding symptom of acute anterior poliomyelitis not observed in epidemic (lethargic) encephalitis, yet Grinker (*J. Nerv. and Ment. Dis.*, October, 1920, iii, No. 4, 323) refers to a curious case that he regards as a combination of acute anterior poliomyelitis and epidemic (lethargic) encephalitis. One year after having influenza the patient had an attack resembling apoplexy, with left-sided spastic hemiplegia. At first there were high leukocytosis and fever, transient sixth nerve palsy and strabismus, hyperemia of the optic nerves, and muscular atrophy of the face and upper limb. Ten days later peripheral facial palsy followed the cerebral paralysis, and there was atrophy of the muscles of the forearm and hand. The left thenar and hypothenar eminences resembled the Aran-Duchenne type of atrophy. Improvement occurred.

These observations tend to show that in epidemic (lethargic) encephalitis the extent of the inflammatory process is exceedingly variable, and that the spinal cord may be affected. Spinal symptoms associated with bulbar signs do not, therefore, afford sufficient evidence on which to eliminate the possibility of epidemic (lethargic) encephalitis in diagnosis, without consideration of the associated factors; neither does the absence of spinal cord involvement lessen the probability of the bulbar symptoms being due to the virus of acute anterior poliomyelitis.

In concluding, the opinion is adduced that epidemic (lethargic) encephalitis is an infectious disease, having a separate and distinct entity that is not to be confused with acute anterior poliomyelitis, from which it differs particularly in the long survival of the virus in the central nervous system. Its course may, therefore, be very irregular, and be attended with remissions and exacerbations extending over

months or years. The differential diagnosis between acute anterior poliomyelitis and epidemic (lethargic) encephalitis will often be impossible to make if only the subjective and objective signs are considered. Much will depend upon the knowledge of existing epidemics and the weighing of circumstantial evidence afforded by the associated phenomena at the onset of the illness as well as before it develops.

PROGNOSIS AND LATE RESULTS (MORRIS GROSSMAN). There have been about 145 cases of epidemic encephalitis on the Neurological and Medical Services at Mt. Sinai Hospital during the epidemics of this disease during 1919 and 1920. A great many of these patients left the hospital soon after the acute infection had subsided, showing some residual symptoms and signs of the disease. After a number of months had elapsed, we felt that it would be of interest to reexamine these patients in order to determine, what, if any changes were still present. With this object in view, this follow-up study was undertaken. Altogether 89 patients were reexamined.

In order to be reasonably certain that none of the symptoms or residual signs found at this reexamination was still part of the acute stage of the disease, at least six months were allowed to elapse before a patient was reexamined. The earliest cases were seen late in 1918, so that some of the patients were examined approximately two years after their acute illness. A complete neurological examination was made in each case.

No attempt will be made to correlate the symptoms and physical findings in this reexamination with those noted during the acute stage of the illness.

The findings in the cases may be grouped under the following headings: (1) Psychic disturbances; (2) tremor and irregular involuntary movements; (3) disturbance in attitude and gait; (4) disturbance in tonus and reflexes; (5) residual symptoms in cranial nerves; (6) pupillary disturbances; (7) epilepsy; (8) other residual symptoms and signs; (9) progressive cases; (10) mortality in these 145 cases.

Psychic Disturbances. Fifty-one of the 89 cases studied showed derangement in their psychic functions in one form or another, and 26 of these 51 cases complained of various degrees of irritability. In 6 of these, the patients had become so irritable since their illness that they quarreled constantly with everybody who came in contact with them. A number stated that they had no desire to associate with anyone, but preferred to be alone. They complained of restlessness. They were easily disturbed and would be startled and frightened at the slightest noise. They complained of being unable to concentrate their minds on any subject, and lacked interest in current events. Their mental reactions were retarded and they were slow in following topics that were being discussed. Slight efforts easily produced mental and physical fatigue. These symptoms were particularly striking in those patients who showed symptoms pointing to involvement of the pituitary, or the basal ganglia.

Emotional instability was present in many of these patients. In the majority it was evidenced in a marked depression. They were easily moved to tears. They worried continually; some because they could not sleep, and others because their various symptoms persisted long after their acute illness was over. A number were worried because they still suffered from drowsiness. A few felt happy and unconcerned; they displayed a feeling of well-being that was not in accord with what their physical examination disclosed. Two of these patients were euphoric and presented a psychomotor activity which was almost equal to that seen in hypomanic states.

There were a number of well-defined fear and compulsion neuroses. One patient, a girl of twenty-three, was in constant fear that she would commit suicide. She would always have to repress the impulse to jump out of a window, or throw herself before a train. A second patient, a man of thirty-nine, was in constant fear of being arrested, even though he felt positive that he had done no wrong. A third man was afraid to stay home alone. He did not know what he feared, but

felt safe if anyone, even a child, would stay in the house with him. He realized how absurd his fear was, but maintained that he could not help or understand it. A fourth patient, a woman of thirty-three, could not fall asleep because she could not keep her thoughts away from people she knew who had died. Another man could not sleep because many details of the work he had done that day would repeatedly be reviewed.

Disturbance in memory, especially for recent events, was a common complaint. One patient, a student in accountancy, found that since his illness, in addition to defects in memory for recent events, he was having increasing difficulty in handling figures.

Changes in disposition were very marked in three children. One, a boy of ten, had a mild attack of encephalitis in March, 1920. Previous to his illness his mother stated that she had great difficulty in managing this child, because he was willful, quarrelsome, and always up to some mischief. Since his illness, he has become docile, obedient, and amiable, and has stopped his quarreling with his brothers and sisters. His physical examination showed a twitching in the muscles supplied by the upper and lower branches of the right facial nerve, and some residua in the other cranial nerves. He had gained 20 pounds in weight. His mental reactions were slow and he resembled a mild type of Froehlich's syndrome. Another boy of thirteen was said previous to his illness in April, 1920, to be an obedient, well-mannered, amiable child, who never had any difficulties with his companions. His attack of encephalitis was very mild, yet his mother states that since his illness, he has become extremely irritable, quarrelsome, willful, and impossible to manage. He finds great difficulty in his studies, and has fallen behind in his school work. He has acquired a spitting tic. Every few seconds he has an irresistible desire to spit, and does so, accompanying the act with an explosive grunt. He states that he cannot control this desire for more than a few minutes at a time. The third child began to steal little things, and tell

many lies since his illness. He had never done these things before. He has become mentally slow, and cannot get along in his school work.

Insomnia was a complaint in 49 of the 89 cases. This complaint is so striking that it must be considered an undoubted sequel of encephalitis. Almost all of these patients stated that it required from one to two hours before they could fall asleep. Until the early morning hours their sleep was easily disturbed. Some of the patients thought that they could not sleep well on account of pains which they suffered. Others, the majority, thought it was due to the fact that they could not relax completely, and that their minds were constantly active. A similar insomnia was noted in many of the patients during the acute stage of their illness. This symptom, therefore, should not be considered a purely psychoneurotic manifestation. Many of the patients complained of excessive drowsiness throughout the day; some of them even fell asleep during their work hours, and were unable to hold their positions on this account. Yet when they went to bed at night, sleep was difficult and in some cases even impossible.

Based on the publicity given the disease among the laity, many patients felt that they had acquired a certain importance in having passed through the dangers from it. These patients felt heroic, yet they craved for sympathy and reassurance.

Tremors and Irregular Involuntary Movements. Fifty-two patients showed either tremor or some form of irregular involuntary movements. They were present in 10 out of 21 cases eighteen months after the acute stage of the illness had passed; in 11 out of 21 cases twelve months after; in 29 out of 42 cases nine months after, and in 2 out of 5 cases six months after the acute illness. Among these 52 patients, there were 25 who showed a fine or coarse tremor of either the lips, tongue, facial muscles, arms, head or lower extremities. These tremors closely resembled those seen in toxic states. The finer ones were like those of hyperthyroidism, and the coarser ones simulated those seen in chronic alco-

holism. These tremors were as a rule not evident when the parts were at rest, but became apparent when the parts were put into action. Ten of the 52 patients showed a tremor that was spontaneous, present while the parts were at rest, and as a rule limited to the distal parts of the extremity affected. Emotional stress caused an exaggeration of the tremor, and it was said to disappear during sleep. This tremor was like those seen in paralysis agitans. In 3 of the cases it was present in both hands; in 3 others it was present only in one hand; in 3 cases the arm and leg were the seat of the tremor, and in 1 case both arms and legs were involved.

Ataxic tremors of the intentional type were noted in 5 cases. In 3 of these patients the tremor was present in both arms; in 1 case the head and both arms were affected, and in the other case it was present in all of the extremities. These tremors were present only when the parts affected were in action. They were characterized by large, coarse, irregular oscillations, with a variable range of movement which tended to increase as the goal was reached. They closely resembled the tremors seen in multiple sclerosis and cerebellar disease. One of the patients in addition to the tremor had nystagmus, scanning speech, and ataxia in her gait. She was however progressively getting better.

Five patients had a rapid clonic twitch of the muscles supplied by one or more branches of the facial nerve. This twitching closely resembled the muscular response obtained when the nerve is stimulated with an electrical current. It occurred every few seconds, was very rapid, and always definitely limited anatomically to the muscles supplied by the particular branch involved.

Three of the patients showed choreiform movements of the tongue, face or extremities. Three others had fibrillary tremors of the tongue; 2 associated with unilateral atrophy of the tongue. One patient showed myoclonic movements of the perineal muscles one year after the acute illness.

Disturbance in Attitude and Gait. There were 14 of the 89 cases who showed disturbance in their attitude and gait.

Four patients showed the typical attitude and gait of paralysis agitans. All 4 were children; the youngest was seven and a half and the oldest was sixteen years. Five other patients showed similar attitudes, but in addition walked with a hemiplegic gait. Loss of associated movements was present in 5 of these 9 cases. Propulsion was present in 4 and in one of these retropulsion was also present. Three patients walked with a spastic paraplegic gait, and 2 patients walked with a right hemiplegic gait.

Disturbance in Tonus and Reflexes. Tonus was disturbed in 17 cases. In 4 of these there was slight increase in the muscle tone. In 5 there was a moderate increase, but not sufficient to produce the "cog-wheel phenomenon." In 5 others there was a marked increase in tonus and the cog-wheel phenomenon was elicited. Two patients had diminished tonus in the muscles of the lower extremities, and one patient had dystonia in the muscles in both thighs.

The deep reflexes were altered in 27 cases. In 11 of these patients, the deep reflexes were greatly increased, but equally so on both sides. In 15 the deep reflexes were unequal, being more active on one side than the other. In one patient the right ankle-jerk was absent and the left diminished, while the knee-jerks were both equally hyperactive.

The Babinski reflex was definitely present in 6 cases and doubtful in one. In 2 of the 6 patients it was present on both sides, while in the other 4 it was present only on one side. Three of these patients presented clinically paralysis agitans features. In one of the patients there was associated with a bilateral Babinski, hypotonus at the ankles, and loss of the right ankle-jerk.

Cranial Nerve and Pupillary Disturbances. There was some disturbance in the cranial nerves present in 57 of the 89 cases. In 36 of these, slight facial inequality was present on one side; 2 others showed bilateral facial weakness. This slight disturbance in facial innervation in the majority of the cases seemed to be supranuclear in origin. Nine of the patients showed both the facial and external rectus involve-

ment; 2 showed involvement of the external rectus alone; 2 showed atrophy of the tongue, and 1 patient had fibrillary tremor without the atrophy of the tongue. One patient showed deviation of the tongue to the right, and one patient had paralysis of the soft palate on the right side. Five of our patients showed some disturbance in the optic nerves during the acute stage of their illness. In this reexamination only one patient was found to have definite changes. This girl had a temporal pallor of the right nerve and almost complete atrophy of the left nerve head. No optic neuritis was noted during the acute stage of this patient's illness. She also complained of diminution of her hearing on the left side, but there were no objective signs of disturbed function present.

Incomplete ptosis was present on one side in 16 patients; it was present on both sides in 7 others. The pupils were unequal in 26 of the 89 cases. Irregularity of the outline of the pupils was noted in 5 patients. Disturbance in the reflex to light or convergence was present in 26 cases. In 10 of these 26 patients there was a sluggish and incomplete reaction to light in both pupils; in 7 others only one pupil was affected. In 4 patients there was a sluggish reaction to light on one side and complete loss of reaction on the other side, with sluggish reactions to convergence in one or both of the pupils. Argyll-Robertson pupils were present in 5 cases. In 3 of these patients it was present on one side only, and in 2 it was present on both sides. One patient, the girl who showed the atrophy in the nerves, had what appeared to be on rough testing, a left homonymous hemianopsia; the pupils in her case were sluggish, but Wernicke's reaction was not tested.

Epilepsy. Three patients suffered from grand mal or petit mal attacks since recovering from their acute illness. The patient with the grand mal attacks had had since his acute illness in January, 1920, 4 seizures in which there was complete loss of consciousness for a period of from five to ten minutes. He also had a great many seizures in which he did not lose consciousness. The other 2 patients, both males, one twenty-seven and the other forty-eight years of age,

have been suffering since their acute illness, from attacks of spasmodic contraction of the right side of the face. These attacks come on at irregular intervals, last from thirty to sixty seconds, and in the older of the two patients are accompanied by vertigo, confusion, and difficulty in speech which lasts from one to two minutes. If standing when the seizure occurs, they must grasp some nearby object to keep from falling. Any number of attacks occurred each day.

Other Residual Signs and Symptoms. Headache and generalized pains in various parts of the body were a most common complaint. The headaches presented no special characteristics; they were located over any part of the cranium, and usually diffuse. Burning on the top of the head and behind the eyes was also a common complaint. The pains in the body and extremities were present in the patients who had suffered from the neuritic form of encephalitis. Some of these patients state that their pains were as severe at the present time as they had been during the acute stage of their illness. Most of them however claimed the pains were less severe.

Exophthalmos was noted in 4 cases. It was present on both sides, and was unaccompanied by any other signs of hyperthyroidism with the exception of tremor of the hands. Tremor of the hands however was present in so many of the patients that it could not definitely be attributed to hyperthyroid activity in these patients.

Increase in weight was noted in 15 cases. In 13 of these the amount gained above the best previous weight was 15, 15, 17, 20, 20, 25, 25, 35, 38, 45, 48, 50, and 95 pounds. In 2 the amount gained was not definitely known. Many of these patients showed some other manifestations of disturbed pituitary function.

Progressive Cases. Seven of the patients showed definite evidence of progression in their disease at the time they were examined. Five of these were of the paralysis agitans type. They showed the typical attitude, gait, tremor, rigidity, and restlessness seen in this disease. In some of these, disturbance

of associated movements was also present. One of the other 2 patients, a male, thirty years of age, has gained since his illness sixteen months ago, 95 pounds in weight; he is always drowsy and mentally sluggish. Six months ago fibrillary tremors and atrophy of the left half of his tongue were noted. He is progressively getting worse. The other patient was taken ill in November, 1919. At that time her physical condition showed bilateral facial weakness, tremor of the tongue, intention tremor and rigidity with cogwheel phenomena in both arms, and the attitude and gait of paralysis agitans. In December, 1920, reexamination showed she walked with a peculiar gait, not unlike that seen in a case of progressive torsion spasm; there were choreiform and choreo-athetoid movements of the face, neck, shoulders, and lower extremities. There was constant uncontrollable grinding of her teeth. While seated, her pelvis and lower extremities were constantly being twisted by involuntary spasms of the muscles. Her pupils were irregular and almost completely immobile in their reactions to light and convergence. There was slight flatening of the facial folds on the right side. Dystonia was present in the muscles of the lower extremities. The deep reflexes were present and equally active on both sides; Babinski was not elicited.

The majority of the other patients admitted that they were gradually getting better. Even though they had many complaints, they stated that these symptoms were far less severe than they were at the time when they left the hospital.

Mortality. Among the 145 patients admitted to the hospital 29 died. This gives a mortality rate of 20 per cent among these patients. Notice of the death of one other patient after she left the hospital was received.

Prognostic Conclusions. Sufficient time has not yet elapsed since the acute illness, neither is the number of cases in this study large enough to warrant drawing absolute conclusions as to what the ultimate prognosis will be in these patients. There are, however, a number of striking facts that might be emphasized.

1. Psychic functions in some form or another were disturbed in 55 per cent of these patients.

2. Insomnia was present in 55 per cent of the cases.

3. Tremor and irregular involuntary movements were present in 58 per cent of the cases.

4. The deep reflexes were altered in 30 per cent, and muscle tonus was disturbed in 18 per cent of the cases.

5. The cranial nerves showed residual signs in 64 per cent of the cases.

6. Pupillary disturbances were found in 30 per cent of the cases; 5 patients showed Argyll-Robertson pupils.

7. About 8 per cent of the cases showed signs of progression at the time they were examined.

8. The mortality among the 145 patients admitted to the Mt. Sinai Hospital was 20 per cent.

From the above findings one might venture the following tentative prognosis. Probably less than 20 per cent of the patients who become ill with epidemic encephalitis die during the acute stage, as usually only the more severe cases reach the hospital. Of those who survive the acute stage of the illness, about 10 per cent may develop a progressive disease of the central nervous system. The remainder will make a good functional recovery in from six to twenty-four months, with the probability of progressive approach to the normal after that period.

The following questions submitted to Dr. Grossman before the commission, together with the answers to them, are here reported *verbatim*.

DR. TILNEY: Would you mind stating the percentage of total recoveries, that is without any sequelae.

DR. GROSSMAN: That is rather difficult because I did not take that up. Most of the patients showed something and it was very difficult to state how many. I did not take that point up specially.

DR. TILNEY: There were no complete recoveries as far as you are able to say?

DR. GROSSMAN: Very few.

DR. SACHS: May I ask Dr. Grossman to make a statement. You say that actual psychoses had not been observed or they were not included?

DR. GROSSMAN: They were not included in this study.

DR. SACHS: Did you observe any?

DR. GROSSMAN: One case which I did not include in this study.

DR. SACHS: Only one psychosis which you could attribute to this disease?

DR. GROSSMAN: Yes.

DR. BARKER: I would like to ask if the patients showing neurasthenic or psychasthenic states after encephalitis were neurasthenic or psychasthenic before? In other words, did these neurasthenias and psychasthenias come as entirely new things in the life of the patient?

DR. GROSSMAN: I went into that question very carefully, and in most of these patients it was stated that they were different after the disease than they had been before. Of course, the actual condition of the patients I am not in a position to state. It is merely the statement of the relatives or the patients themselves that I have to go by.

DR. BARKER: Another question I would like to ask is whether or not there is going to be any way of distinguishing between these patients with residual Argyll-Robertson pupils and patients who have Argyll-Robertson pupils due to a burnt out tabes?

DR. GROSSMAN: There is only one way, that is to take the general picture into consideration. One or two of these patients had no other evidence except the Argyll-Robertson pupil—no other evidence of the disease anywhere. Without the Wassermann test it would be difficult.

DR. SACHS: May I ask one more question? Did you make this statement that the residual headaches were generally occipital?

DR. GROSSMAN: No. My statement was that they occurred in any part of the head; there was no distinctive localization. Some complained of one part and some of another—different parts of the head. There was no grouping that one could make.

DR. TAYLOR: Was the atrophy of the tongue unilateral or bilateral?

DR. GROSSMAN: Unilateral.

DR. TAYLOR: In a general way, what was the age of the patients who had increased in weight?

DR. GROSSMAN: The ages vary. Many of them were children. One man, I believe, was thirty years of age, but the majority of the patients were in the younger groups. These were abnormal increases, such that the parents of the children themselves noted it. They wanted to know why it was that these children had increased so rapidly. It was a rapid increase in weight noticeable to the parents of the children, disproportionate to their growth.

DR. DANA: I do not know whether it is not true that in children who have acute infections and get over them there is not sometimes a rapid increase in growth—in any kind of infection.

DR. GROSSMAN: That may be true but this increase occurred in only a limited percentage of these children, so much so that it was evident to the parents, and was a point that they themselves volunteered. I did not ask for it. They said these children were growing abnormally stout in a short time. It was a growth of fat, as a rule. This covers a study of six months to two years. That varies; in different individuals the study extends over two years.

DR. SACHS: But the increase in weight was chiefly, as I understood it, after the illness?

DR. GROSSMAN: Shortly after the illness. It was usually associated with mental sluggishness. These children, as a rule, became backward in their studies; they didn't seem to be interested, and they were inclined to be drowsy and disinclined to any physical activities.

DR. DANA: Would you consider this increase in weight a pituitary symptom?

DR. GROSSMAN: It struck me as if it might be on account of this sluggishness and general lack of interest in any type of work. In one patient there was no doubt in my mind that it was a pituitary condition; there were headaches with it and various other phenomena.

DR. TIMME: Have you noticed in any cases a general muscular atrophy?

DR. GROSSMAN: I have not noticed it in any of these cases.

FURTHER OBSERVATIONS IN PROGNOSIS (JUNIOUS W. STEPHENSON). These conclusions were based on a study of 95 cases observed at the Neurological Institute and Bellevue Hospital, New York City. Sixty of the cases had been recently examined by the author, and of the remaining 35, a majority reported their condition through correspondence.

No case was considered in which the illness had not extended over a period of six months, the large majority being nine to twelve months. According to the predominant symptoms, the cases were classified as follows: Parkinsonian type, 33 per cent; spinal type, 20 per cent; cranial nerve and diplopia type, 20 per cent; cerebral type, 10 per cent; mixed type, 17 per cent.

Parkinsonian Type. All the cases examined showed improvement, but no case showed a complete recovery. One case reported no improvement. Fully 75 per cent complained of various functional symptoms, such as head and spine pains, fatigability, lack of concentration and other neurasthenic symptoms. No actual obsessions were encountered. The functional symptoms almost invariably appeared between the third and fifth month after the onset of the illness. One case developed a psychosis. This patient suicided nine months after the onset of illness. One boy, eight years of age, five months after the onset of illness, showed evidence of moral derangement. This boy, prior to the illness, had been a model child, but now was given to thieving, lying and even attempted arson. He showed one testicle considerably smaller than the other, but the mother could not state whether or not that existed prior to the illness. It was observed that in those cases in which there were gross tremors associated with lethargy, when improvement did begin, it progressed more rapidly than those which showed fine tremors. There was one distinct relapse. This patient, a woman thirty-five years of age, five months after the onset of the illness, was in condition so that she could perform her household duties in a normal manner. Later, she gradually became "dopey" during the day, and wakeful at night. In addition, her tremor became more aggravated, and whereas her mask-like expression had almost disappeared, upon examination she showed a distinct masked facies. Objectively all the cases showed rhythmic tremors of varying degrees, with hyperactive reflexes. There appeared a tendency for the mask-like expressions to clear up.

Spinal Type. With the exception of two, all showed a slowly progressive improvement, but none was free of symptoms. The disappearance of symptoms was in the following sequence: myoclonia, tremor, pain. In practically all the cases, sticking pains were at times distressing. It was observed that in those cases beginning acutely with moderate temperature and severe pains, improvement, when it began, was more rapid than in those in which onset was subacute. There were two distinct relapses, and in both cases, the relapse occurred about five months after the onset of the illness. One, a man thirty years of age, had a recurrence of pronounced intensity; severe pains, gross myoclonus and tremors. His deep reflexes were hyperactive, but he showed no distinct pyramidal disturbance. The original onset of this case was very slow; the relapse quite acute. The other, a girl seventeen years of age, in addition to the clinical picture of the original onset, now showed typical trophic sores, and whereas previously her deep reflexes were overactive, they were now very sluggish. There was some impairment of her joint sense inasmuch as at times she was very much confused in recognizing the position of her toes. Vibratory sense was intact. In both cases "sticking pains" were extremely distressing. Up to the time of the relapse both cases showed slow but steady improvement. Sequelae of functional type were also observed in these cases, but less frequently than in the Parkinsonian type.

Cranial Nerve with Diplopia Type. This type represents that class in which objective findings revealed multiple cranial nerve involvement with diplopia. The onset in the majority was more or less acute. The diplopia persisted from a few days to six weeks. Of the cranial nerves the sixth was the first to clear up. The most persistent objective finding was a thalamic facies. In the majority of cases that had shown slowness of light reaction, there was a gradual return to normal. No relapse was observed. No functional sequelae were observed. Improvement in this class was more rapid than in any other of the types quoted, and apparently this

particular type will ultimately prove the most favorable so far as complete recovery is concerned.

Cerebral Type. This type included those cases showing hemiplegias, aphasias and other distinctly cerebral manifestations. None had completely recovered, but in all there had been a gradual but very slow recovery, both subjectively and objectively. Two cases which had previously shown a papilledema were now free of it. Where the onset was acute and the illness profound, if the individual survived the acute symptoms, recovery was more rapid than in the less acute cases.

Mixed Type. This included any combination of the above types, and pursued a course concomitant with the type predominating.

Mortality. Of a series of 57 cases in Bellevue Hospital there were ten deaths, giving a mortality of approximately 20 per cent. Of the ten deaths, four were adults and six were children below the age of ten. Of 38 cases recorded at the New York Neurological Institute, there were four deaths: three adults, one child. In those children in whom death occurred, the onset was acute, with high temperature and delirium, and the average duration of the illness was seven to eight days. In the adults, the symptoms were not so acute, nor was there such a pronounced rise of temperature, and the duration of the illness was from ten days to six weeks. It was observed that adults showed a rather constant mortality of approximately 10 per cent, whereas children approximated 15 per cent.

This disease presents so many different clinical pictures (the three epidemics being entirely different from one another) that at this time no one can formulate any definite prognostic data. However, the disease does show a distinct tendency to a spontaneous improvement, but in my opinion a period of from two to three years was necessary to determine just to what degree improvement would progress; though relapses do occur, they are infrequent. I am apprehensive that the Parkinsonian and spinal types would undoubtedly augment

our existing army of neurasthenics. It is my opinion that psychotic sequelae would be infrequent. The more acute the onset, the more rapid would be the improvement. The grosser the tremor in the Parkinsonian and spinal types, the more rapid the improvement. Papilledema occurring during the disease shows a tendency to spontaneous subsidence. The cranial nerve and diplopia type offers the most favorable outlook. The mortality can be fairly accurately estimated for adults as 10 per cent; for children under the age of ten, approximately 15 per cent.

The following questions submitted to Dr. Zabriskie before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask whether Dr. Zabriskie thinks from his own experience or the experience of others that frequent lumbar punctures have really been of some benefit?

DR. ZABRISKIE: It has not been my experience, and as far as I can find in the literature the opinions vary greatly, but the preponderance of opinion is that they have no specific effect.

DR. SACHS: It has not even hastened the period of recovery?

DR. ZABRISKIE: Some have reported that it has but for the most part I think not.

DR. TAYLOR: May I ask how your atropine has been administered?

DR. ZABRISKIE: Both by mouth and intravenously.

DR. TAYLOR: And what has been the result—either yours or the experience of others?

DR. ZABRISKIE: My own experience has been entirely by mouth. The only note I have been able to find on that has been among the French in which they recommend the mouth method as preferable to the intravenous because of the more rapid elimination by the intravenous method.

DR. TAYLOR: How about the arsenical preparation?

DR. ZABRISKIE: There have only been a few cases reported of that, and one man reports beneficial effects. I have forgotten his name. Netter disapproves of it because he found bad results in 2 cases, I think.

DR. TAYLOR: Do you feel that any of these things have done any good really?

DR. ZABRISKIE: None of them. One recommendation I have found is the rather cruel method of fixation abscess. Netter reports 79 cases; in 52 the abscess was used, and in 27 the abscess was not used. His results were ten deaths with the abscess and thirteen deaths in the cases without abscess. Of those ten deaths with the use of the turpentine injection, six did not go to abscess formation, and therefore he discards them. Of the remaining four, two died before the abscess had had time to develop, and that only left two deaths in which the abscess had formed, and both those deaths were in pregnant women.

DR. SACHS: Have there been any distinct reports regarding the use of the serum from convalescent patients?

DR. ZABRISKIE: That has been tried and on the whole unfavorably reported upon. I mean to say reported unfavorably in the sense that it apparently had no influence on the patient. They were all injected intraspinally.

CONCLUSIONS OF THE COMMISSION

1. *Diagnosis.* Up to the present time through lack of definite criteria separating epidemic encephalitis as an entity from all other disturbances, a great many cases of the disease may possibly be of such mild character, or may occur in moderately immune individuals, that the development of the affection may never reach the degree of maturity expressed by neuropathic or psychopathic states, and hence in the classification advanced in this chapter such possible cases find no group to which they may become attached. There is, therefore, still to be sought the basic criterion. For those cases that have clinically been recognized as epidemic encephalitis, the foregoing classification seems to the Commission to be sufficiently definitive and adequate in scope.

2. *Differential Diagnosis.* A similar statement may be made here as to our inability to separate mild and abortive cases of epidemic encephalitis from other conditions which they simulate. Thus, influenza may have various neuritides as accompaniments or sequelae, as well as psychopathic states.

The spinal fluid pleocytosis is not a necessary factor in epidemic encephalitis and hence cannot be accepted as a strictly differential point. Even more difficult, if not impossible, would be the diagnosis between epidemic encephalitis and certain forms of anterior poliomyelitis. This difficulty is well brought out by the special paper on the subject.

The Commission would therefore submit that only in the moderately well-marked cases of either disease is the diagnosis fairly easily made, but that in formes frustes, or in mild types, the diagnosis at the present state of our knowledge might well be impossible.

3. *Prognosis.* The opinion of the Commission upon this phase of the research problem is that for the number of cases examined by two independent observers, the results are sufficiently uniform to be tentatively accepted until such time as a much greater number of patients shall have undergone examination. One fact, however, must be borne in mind. All the cases examined were severe hospital cases and hence the Commission feels that the mortality rate as given, as well as the other rates, should properly be limited in their application to "severe hospital cases." The total number here reported is only about 170. Furthermore, a longer time must have elapsed from the onset of the disease to the examination period. In the meanwhile, however, the conclusions given seriatim by Dr. Grossman at the end of his paper seem well grounded. The mortality of the disease is given as from 10 to 20 per cent by both observers for the acute stage of the disease. The Commission regrets the absence of figures giving the number of cases that presented no sequelae whatever; in other words, complete recoveries. The consensus of opinion, however, is that these are very few. About 8 per cent of the cases examined showed signs of progression of the symptoms. It must be remembered, in going over these papers, that the cases represented are practically all severe ones with marked symptoms of involvement of the central nervous system. Many of the milder forms, the Commission believes, never reached the hospitals,

and many of these in all probability had no sequelae of importance.

The cases of recrudescence of the symptoms in the course of the disease are discussed in the chapter on symptomatology.

4. *Treatment.* Not knowing the causative factors involved in the pathogenesis of epidemic encephalitis, it becomes impossible at present to outline a rational therapy. And so, from no treatment, through the entire gamut of remedial agents to the medieval "fixation abscess," everything seems to have been essayed. There are no statistical tables available for comparison as yet and no individual treatment has been extolled even by its originator to a degree which warrants closer examination of the returns. For this reason, the Commission feels itself constrained to make no report upon the merits of any particular method of combating the disease. There likewise seems no basis for a rational preventive therapy other than a non-specific one applicable to all diseases of infectious character.

CHAPTER VI

MORBID ANATOMY: PATHOLOGY OF THE BRAIN AND SPINAL CORD; LESIONS OUTSIDE THE NERVOUS SYSTEM

IN the chapter on the pathology of epidemic encephalitis the commission submits its opinion concerning the gross and microscopic alterations caused by this disease. This opinion is based upon the reported investigations of Dr. James B. Ayer of Boston, covering the gross and microscopic lesions in the nervous system; of Dr. William G. Spiller of Philadelphia, dealing with the detailed pathological changes in five brains and two spinal cords; of Dr. Hubert S. Howe of New York, describing the microscopic appearance of the several endocrine organs; of Dr. William Boyd of Manitoba, Canada, revealing the pathological alterations in parts of the body other than the nervous system; and of Dr. George B. Hassin of Chicago, contrasting the histological changes in the nervous system due to epidemic encephalitis with those due to lead and other poisons.

This section of the report also includes the questions submitted by the Commissioners to the investigators mentioned above, together with the answers made during the public hearings of the Commission. In many instances the answers to the questions proposed by the members of the Commission shed much light upon points in the investigation which might otherwise remain obscure or in doubt. For this reason it has been deemed advisable to reproduce the verbatim report of the questionnaire and responses of each investigator.

The Commission brings this section of its report to conclusion by a summary of what it considers to be the well-

established facts in the present state of our knowledge concerning the pathology of epidemic encephalitis. It has also undertaken to express its opinion regarding certain defects in this knowledge and to point out the steps which may be taken to overcome such defects.

THE GROSS AND MICROSCOPIC PATHOLOGY IN THE NERVOUS SYSTEM (JAMES B. AYER). *Material.* In a disease of such diverse symptomatology, and presenting so great variations in severity and duration of the clinical course, it is surprising that the pathological findings have been so nearly uniform.

The material upon which the report is based represents the necropsy findings as published during the period 1917-20 from the following countries: Austria and Germany, 16 cases; Switzerland, 4; France, 10; England, 39; Rumania, 1; Canada, 9; United States, 34; a total of 113 cases. The reports from Australia have been omitted from this summary. It was surprising to find how few pathological reports are on record, considering the mortality of the disease, and to what extent the authors of clinical articles have copied the findings of a very few investigators. For general description all of these 113 cases are useful, but for fine histological comparison and topographic orientation a much smaller number, not more than 50, is available.

Gross Appearance of the Brain and Spinal Cord. On inspection the brain has with few exceptions been found to be markedly congested, at times so intensely as to be uniformly pink in color, both large vessels and capillaries being greatly engorged. Free blood is seen in the sulci, and occasionally minute hemorrhages over the gyri, but massive pial hemorrhage is seldom seen. The pia-arachnoid is frequently described as edematous. Rarely are the convolutions flattened. The dura mater has shown no lesion. If variation in the intensity of the meningeal congestion has been noted in different loci, the most intense has been over the brain stem, and the least over the cerebellum. The spinal cord, when

wholly removed, has frequently shown a similar vascular congestion, always less intense than that about the mesencephalon and fading out caudally. On section the cut vessels are everywhere prominent, both in the brain and cervical cord, but especially in the gray matter of the basal ganglia, mid-

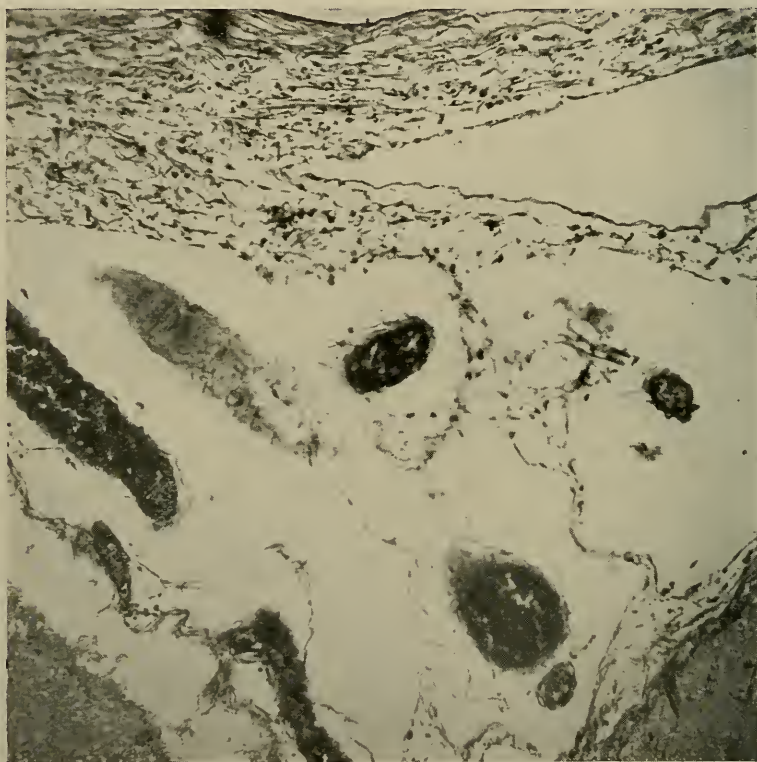


FIG. 10. Cortical meninges from an acute case, the patient dying supposedly five days after the first symptoms. Arachnoid trabeculae sparsely infiltrated with mononuclear cells and blood corpuscles. Pial vessels greatly engorged. $\times 66$. (Wegeforth and Ayer, *J. Am. M. Assn.*, July, 1919, p. 14.)

brain and pons, in which loci minute hemorrhages are occasionally seen. The tissue is uniformly softer than normal. Ventricles are normal in size and contain cerebrospinal fluid of normal appearance; the ependyma is usually smooth and glistening, but occasionally has been a little roughened.

Microscopic Appearance; Infiltration and Hemorrhage. Microscopically the most striking type of lesion is cell

infiltration. The vessels chiefly affected are small veins, but larger veins, arteries and capillaries are not immune. The cells are almost always mononuclear lymphocytes, plasma

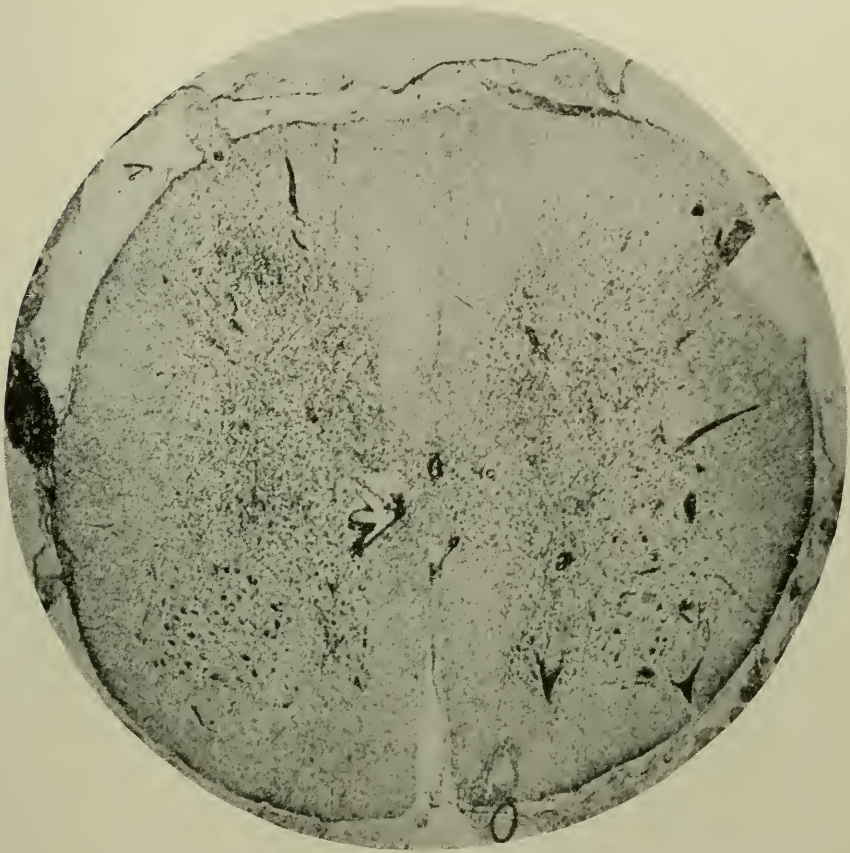


FIG. 11. Lumbosacral portion of the spinal cord (Case 3). The membranes are slightly infiltrated; the subarachnoid space shows on the left a congested vein; the anterior and posterior horns exhibit a number of infiltrated vessels; the number of ganglion cells in the anterior horns is normal; the ependyma cells of the central canal are proliferated (a magnifying hand-glass will show the details better). (Toluidin-blue stain, $\times 16$.) (Bassoe and Hassin, *Arch. Neurol. & Psycho-Path.*, 1919, ii, p. 16.)

and large nononuclear cells, the latter of doubtful endothelial or mesothelial origin. These cell infiltrations are typically seen to be confined to the vessel walls, the Virchow-Robin and perivascular spaces. There is general agreement

that this type of pathological process is most intense and most extensive in the gray matter of the basal ganglia, midbrain, pons and medulla, and the cervical cord. The

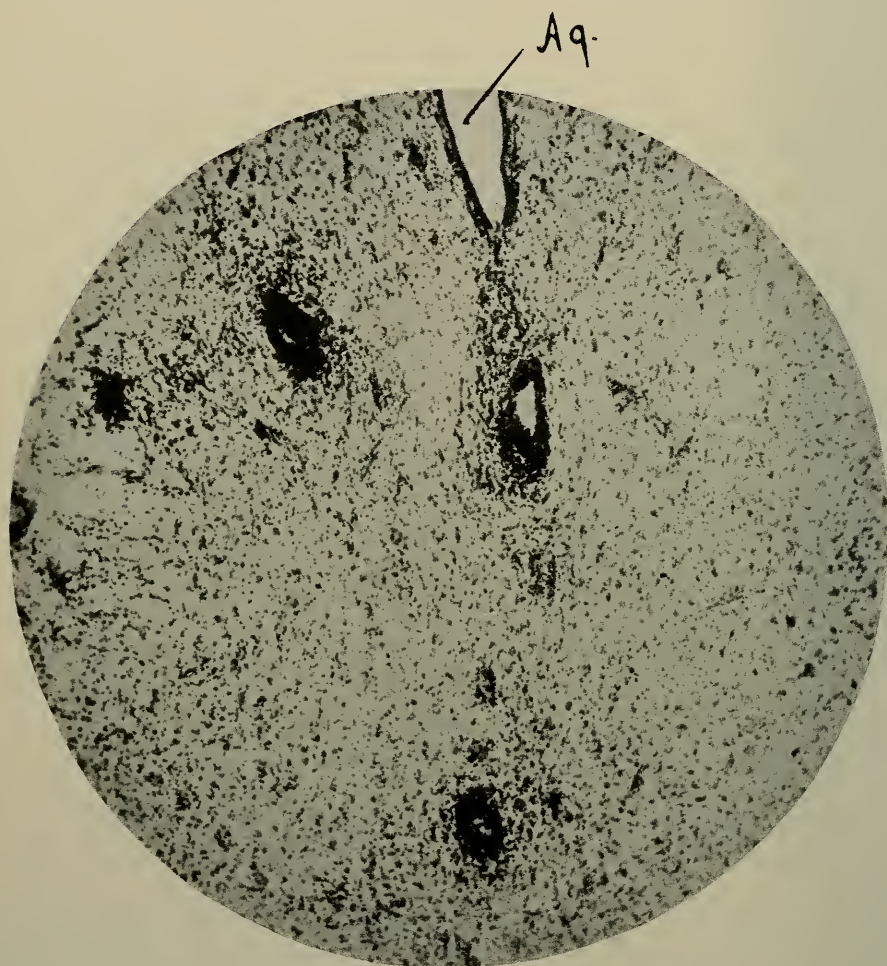


FIG. 12. Tegmentum of pons. Aq. Aqueduct of Sylvius. Toluidin blue, $\times 65$. Three types of lesions are shown: perivascular infiltration, diffuse infiltration of the nervous tissue, and proliferation of the subependymal neuroglia. (Bassoe and Hassin, *Arch. Neurol. & Psycho-Path.*, 1919, ii, p. 11.)

region about the aqueduct of Sylvius is most affected while the severity of the process lessens cephalad and caudad. The vessels are described as affected in a patchy manner, some intensely infiltrated, some normal in appearance. The vessels

of the gray matter are chiefly involved while those of the white are by no means immune. In the same territory, and frequently in apparent connection with the above described infiltration, occurs, in almost every case, the second most striking type of lesion, namely, diffuse infiltration of the nervous tissues. The same types of cells are here seen scattered through and intermingling with the fixed cells and



FIG. 13. Hemorrhage into the perivascular space of His, region of thalamus. This is the type of hemorrhage commonly observed in this disease. (Tilney and Riley, *Neurol. Bull.*, 1919, ii, p. 127.)

fibers constituting gray and white matter. Not infrequently large mononuclear phagocytes are found in these territories, and with special stains free fat droplets are here visible. This diffuse infiltrative process is usually described as being most intense in and near the substantia nigra. It is interesting and important to note that, with rare exception, polymorphonuclear leucocytes are not present.

Hemorrhage, as has been stated, is not regularly noted in the gross appearance. Microscopically, hemorrhage into

the perivascular space of His is seen frequently; rarely, however, does it spread from this locus into the nervous tissue. While hemorrhage may occur from vessels showing

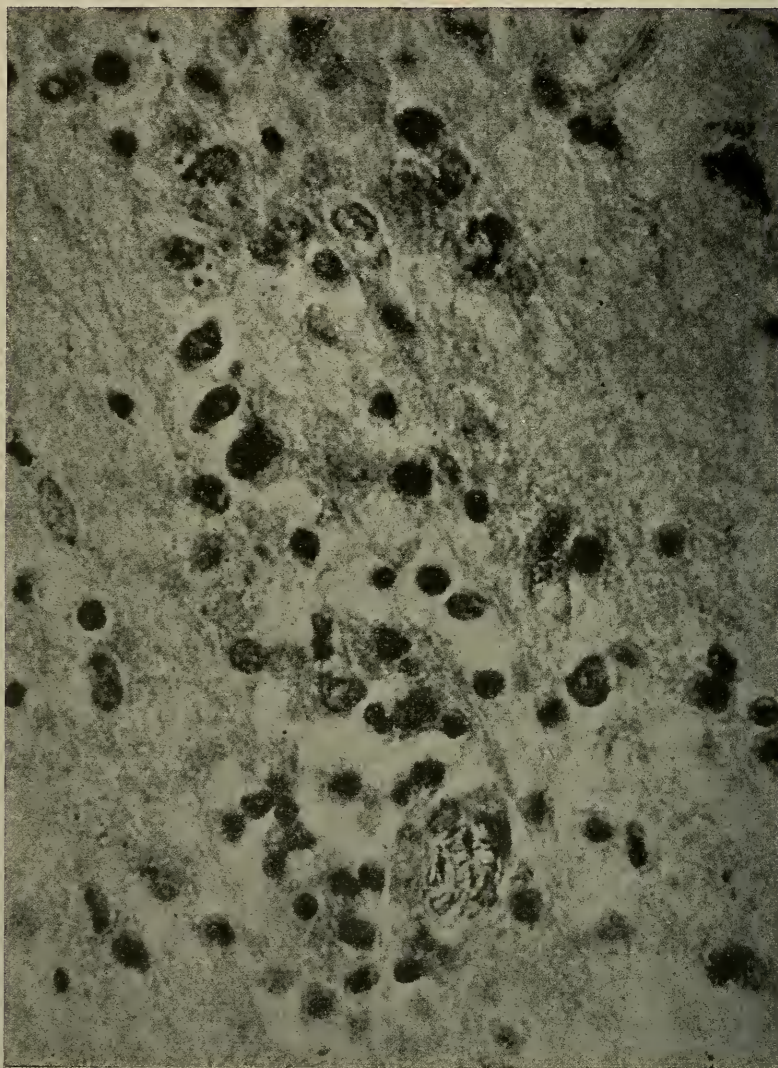


FIG. 14. Midbrain, $\times 720$: diffuse infiltration with plasma cells and lymphocytes. (Wegeforth and Ayer, *J. Am. M. Assn.*, July, 1919, p. 21.)

perivascular cell infiltration, this is not necessarily so. Nor is hemorrhage associated with any marked degree of vascular disease, as indicated by minimal changes in the intima and elastica, and almost total absence of thrombosis during the

acute state of the disease. Where hemorrhage into the parenchyma is seen, it is usually not accompanied by reaction of the surrounding glia.

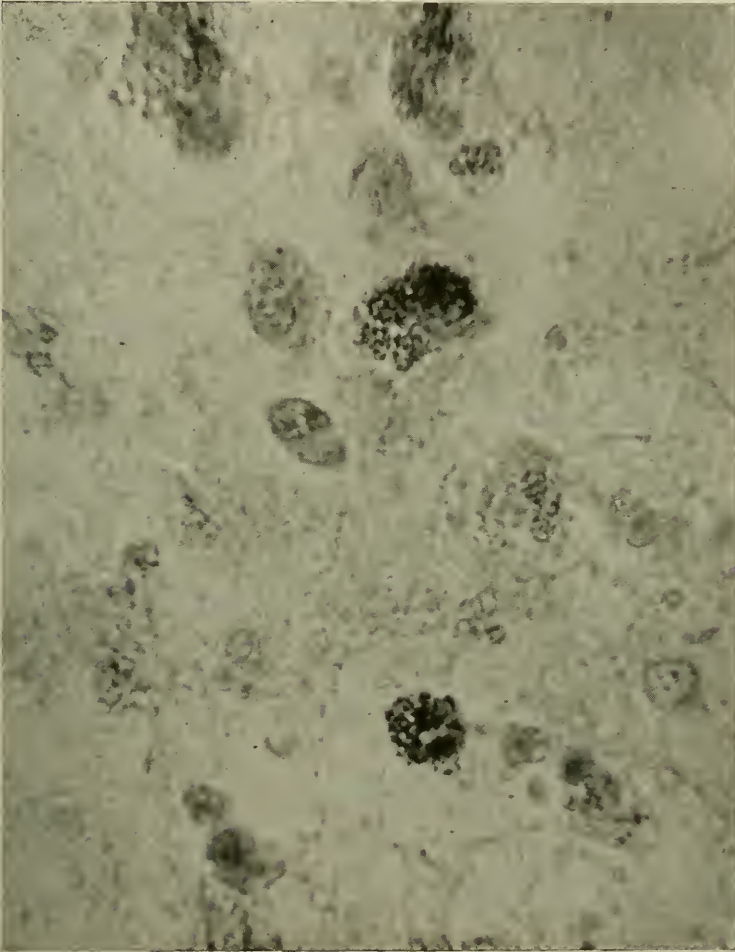


FIG. 15. Midbrain, $\times 1060$. Mononuclear phagocytes and plasma cells in white matter. Death twenty-nine days from onset of symptoms. (Wegeforth and Ayer, *J. Am. M. Assn.*, July, 1919, p. 23.)

Changes in the Nerve Cells and Neuroglia. In discussing changes in the nervous tissue itself, nerve cells, nerve fibers and neuroglia, there is considerable difference of opinion. This is but natural, considering the difficulty in adequately estimating abnormalities of these structures. The majority

of writers evidently have not studied these tissues with thoroughness; hence our knowledge of parenchymatous lesions depends upon the reports of a very few careful workers.

The nerve cells unquestionably show relatively little evidence of degeneration considering the severity of the pathological process. Intense generalized destructive pro-



FIG. 16. A destroyed ganglion cell from the subthalamic region surrounded by plasma cells. (Toluidin blue, $\times 1200$.) Neurophagia is absent in many of the cases reported; it is more likely to be seen in cases of several weeks' duration. (Bassoe and Hassin, *Arch. Neurol. & Psycho-Path.*, 1919, ii, p. 14.)

cesses throughout the brain or the spinal cord have not been described, and only rarely have focal degenerations of large extent, as seen in certain other types of encephalitis, been observed. In areas of greatest inflammation, nerve cells appear apparently intact in the midst of extensive mononuclear cell infiltrations. In the neighborhood of such territories minor changes, such as chromatolysis, are usually

described. However, isolated examples of cell destruction, chromatolysis, swelling of the cell, excentricity of the nucleus, absence of neurofibrils, satellitosis, and even neuronophagia are described in areas of intense infiltrations. In territory free from the striking changes of the disease, such as the cerebral cortex and cerebellum, nerve cells of all types are usually found to be normal or to present minimal degenera-

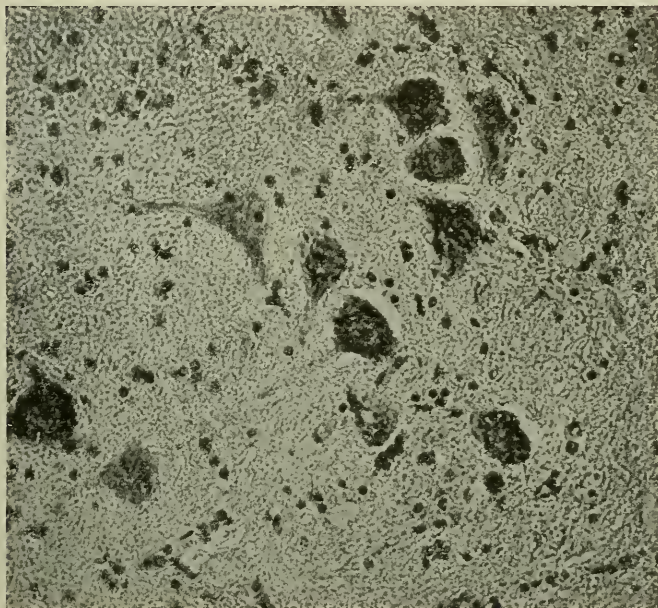


FIG. 17. Hypoglossal nucleus. Many of the nerve cells appear normal, but some are degenerated. The nucleus was infiltrated with ameboid gliosis cells. (Tilney and Riley, *Neurol. Bull.*, 1919, ii, p. 127.)

tive changes; however, complete degeneration of the smaller pyramidal cells and of Purkinje cells, with or without neuronophagia, occurs.

Neuroglia cell proliferation is said to be very considerable in and about areas of intense cellular invasion, and about vessels presenting marked perivascular infiltration. In the cortex and subcortex, also, diffuse neuroglia proliferation of the small cell type is evident in proportion to the amount of nerve cell destruction. Multinuclear forms are not described,

nor is there evidence of neuroglia fibril formation on a scale to warrant comment.

Microscopic Changes in the Meninges. Pia and arachnoid may be normal. Usually, however, besides greatly engorged



FIG. 18. Pial vessels during the acute stage. (Resorcin-fuchsin, $\times 60$). The elastic membrane in the form of solid rings is very clear. In the acute stage the intima also is normal or only slightly affected, vascular lesions being almost confined to the adventitia. (Bassoe and Hassin, *Arch. Neurol. & Psycho-Path.*, 1919, ii, p. 7.)

vessels, already noted in the naked eye examination, the layers of the pia and the reticular network of the arachnoid are separated and in the interstices are numerous red corpuscles and large mononuclear cells. In the depths of the sulci intrapial extravasations of red corpuscles are occasion-

ally observed. Except in these latter areas polymorphonuclear leucocytes are lacking.

Summary. The locus of the most intense reaction is a matter of general agreement. The brain-stem bears the brunt of the attack in almost every case. That the gray matter in gen-

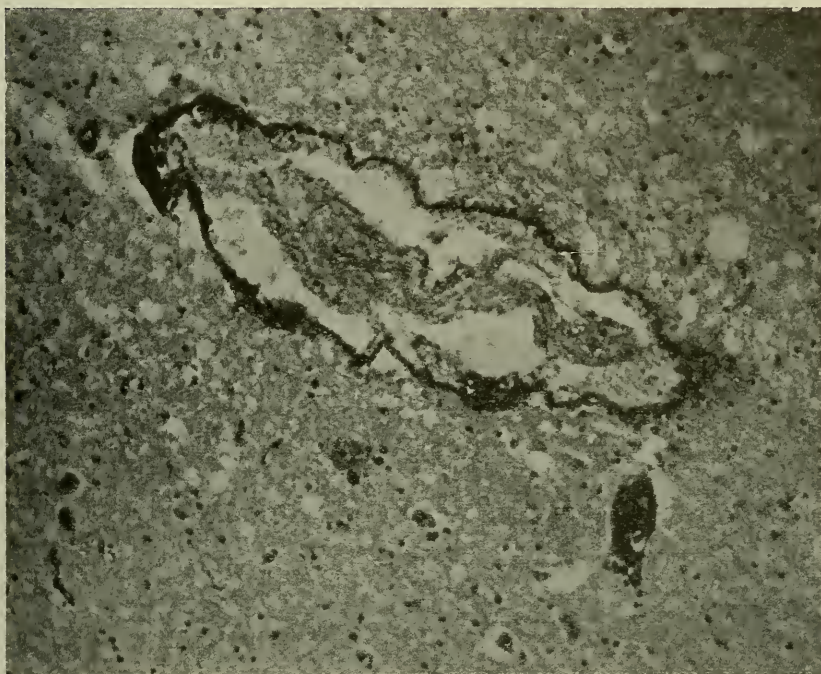


FIG. 19. Basal ganglia. Medium-sized vein showing thrombosis and calcareous degeneration of its walls. (Zeiss 16 mm. obj. Comp. ocular No. 4.) From a case dying four months following the acute attack. The patient was a young woman, and it is unlikely that the lesions in the vessels which were widespread should be attributed to other cause than the preceding encephalitis. (Buzzard and Greenfield, *Brain*, 1919, xlii, p. 330.)

eral is the seat of greatest inflammation is certain, but that the cranial nerve nuclei are especially affected has not been apparent in all cases. The inflammatory process is not by any means limited to the gray matter, either of the brain or spinal cord.

There is agreement that the pathologic process concerns primarily mesodermal structures, that infiltration of the

smaller vessel walls and their true perivascular spaces by lymphocytes, plasma cells and large mononuclear cells is constant; that diffuse infiltration of the gray matter chiefly, but also of the white, is usually present. Also constant, but less striking, are changes in the ectodermal tissues, degenerative changes in the parenchymatous elements, with associated proliferation of neuroglia cells. The changes observed in nerve cells and neuroglia, while most intense in areas of infiltration, may also be seen apart from any inflammatory foci. There is agreement also that the blood-vessels, while universally engorged, remain relatively intact (until very late in the disease), as evidenced by almost total absence of large or frequent hemorrhages, thromboses and microscopic evidence of degenerative or proliferative processes in their walls. The meningeal reaction is also constantly minimal in degree.

Microscopical Changes in Nerve Roots, Cranial Nerves and Dorsal Root Ganglia. Examination of the cranial nerve roots has been carried out especially by Burrows. In each of three cases (two of them typically lethargic and one polyneuritic) he found lesions in several of the cranial nerves, the 2nd, 4th, 5th, 6th, 7th, 8th being affected. The lesion is described as a perivascular lymphocytic infiltration and an interstitial infiltration of the nerve fibers by lymphocytes. Perivascular infiltration of the optic nerve was observed by Mills and Wilson and of the 12th nerve by the writer.

There is almost nothing written on the subject of spinal nerve roots and root ganglia, an omission of importance in view of the fact that in poliomyelitis the ganglia so frequently show marked changes.

Microscopical Changes in Cases of Long Duration. A case of four months' duration reported by Buzzard and Greenfield showed marked change in the pathological picture. The vessels had irregularly thickened walls, frequently with calcareous plaques. The lumen was often closed by fibrous or fibrinous occlusions. This was true of the vessels of the cortex and meninges as well as of those of the brain-stem.

Neuroglial proliferation was marked. Perivascular cell infiltration was likewise present and the nerve cells showed a minimal amount of damage.

Von Economo has published the report of a patient dying a year and nine months after the onset of the illness. In this case the vessels showed thickened walls and thrombi, and the neuroglial proliferation was marked.

PATHOLOGY IN RELATION TO CLINICAL TYPES OF THE DISEASE. With the original conception based upon the first described cases of von Economo and Netter, lethargic encephalitis must necessarily be accompanied by lethargy, oculomotor palsy and perhaps other cranial nerve affection, and a pathologic picture was presented which was considered pathognomonic. It was not long before cases with very different clinical picture presented themselves—epileptiform, choreiform, hemiplegic, polyneuritic forms. One would *a priori* think that entirely different pathological lesions, both as to type and as to distribution, would be required to account for such diverse and contrasting clinical pictures. On the contrary, examinations of the records of published cases, including most if not all of the clinical types of epidemic encephalitis, fail to show great variation in pathology. Certain irregularities as to distribution do occur, but it appears that the same pathological lesions varying somewhat in proportion are constant findings. So that whatever the clinical type, the pathological picture described in the first section of this paper is pretty certain to be found with modifications only as to intensity and locality of the different types of lesions.

Certain of the clinical findings and clinical types of the disease are readily explained on the basis of the pathological changes noted. The cranial nerve palsies occurring in the common forms of the disease are readily explained by the marked infiltration in the nuclei, with or without destruction of nerve cells; in some cases a second possible explanation for the palsy has been shown in the infiltration of the nerves

themselves. In the hemiplegic and apoplectic forms, confluent petechial hemorrhages, either in the subcortex (Buzzard and Greenfield, 2 cases; Boyd, 1 case), or in the peduncle (Wilson) have adequately accounted for the symptoms. Cases with excessive meningeal symptoms have been shown to reveal profound congestion, frequently with considerable pial hemorrhage, and at times excessive mononuclear cell infiltration of the pia (Da Fano, Neal, Schwartz). The anterior poliomyelitic forms have been adequately explained by appropriately placed inflammatory reactions in the spinal cord (Calhoun).

While necropsies on psychotic, choreopsychotic, delirious, catatonic, myoclonic and paralysis agitans types have been recorded, and some of the reports are carefully prepared, there is not enough distinctive in them to warrant drawing conclusions as to the explanation of the peculiar symptoms. In fact, any of these reports might pass as descriptive of a typical lethargic case. Most reports have evidently been compiled with no especial reference to a pathological explanation of clinical syndromes. But even when this has been attempted no distinctive differences appear to have been encountered. For example, Bassoe, commenting on the pathology of two personal cases of the delirious type, says: "It will be noted that essentially the changes are the same as in the ordinary lethargic form."

The following questions submitted to Dr. Ayer before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: May I question Dr. Ayer especially with reference to one statement which he made, which I think was a striking one? I think we ought to ask whether any gentleman here has had autopsy findings in these cases and whether we are actually going to accept it as a fact that in this disease the cortex is the part least involved.

DR. AYER: That has been universally so. I have not seen a single case where the cortex was said to be involved as much

as any other part, and it is always involved very much less; in many cases the cortex is negative. I would like to qualify that remark a little. The cases are not always differentiated pathologically, but all types have fallen under the pathological hammer. One would expect to get more cortical changes relatively, but this has not been the case. With all the types that may have died from bulbar lesions taken into account, they all look about the same and there is little to choose in them.

DR. SACHS: The important inference would be that the lethargy has nothing to do with the cortex.

DR. AYER: That is one problem that might be called physiological pathology, perhaps. We do not know much about it. There is this tremendous engorgement of the vessels, and many of the symptoms, such as delirium, may be due to pure engorgement of the vessels. That is a thing we have no means of checking up. And so this fluid state—the cerebrospinal fluid and the blood—may play a large part which when we look at it pathologically, we cannot judge. All we can say is that in every case the one thing that stands out is the engorgement of all vessels especially at the base of the brain.

DR. TILNEY: Is it not also true that the investigation of the cortex has been thoroughly inadequate and will not justify any comparative statement at the present time? Merely pieces of cortex have been taken here and there, and we can not guarantee any statement as to the relative cortical involvement.

DR. AYER: As a rule one or two pieces are examined, and then the cortex is put down as negative. Very few articles have really as yet adequately covered the whole brain.

DR. PRINCE: Has serous infusion in ventricles ever been found?

DR. AYER: The ventricles almost always have been normal in size and have been found to contain the normal amount of fluid.

DETAILED PATHOLOGICAL REPORT OF THE BRAINS OF FIVE CASES AND THE SPINAL CORD FROM TWO OF THESE CASES (WILLIAM G. SPILLER). *Changes in the Cerebral Cortex.* The pathological changes in the paracentral lobules were slight in all five cases; there was slight infiltration of the pia with mononuclear cells, and some of the Betz cells showed distinct chromatolysis, but in most of the cases these cells could hardly be considered abnormal, especially as the

necropsies were not done very soon after death and formalin hardening was employed. There was little infiltration of the cortex with mononuclear cells. Neuronophagia was distinct. On the whole the changes might be regarded as relatively insignificant. The findings in other parts of the cerebral cortex were similar.

Changes in the Basal Ganglia. The basal ganglia were examined in their lower portion. Much infiltration with mononuclear cells of lymphocytic type and plasma cells was found in all five cases, and the collections of cells were greater in some places than in others. In two cases the infiltration was less than in the other three, and one of these two was a case of the myoclonic type. The condition was like that in the cerebral peduncles but was less intense. In one case the ependymal cells showed an extraordinary appearance in one place; they were proliferated and massed one upon another. The infiltration in the case of the myoclonic type was diffuse and not nearly so intense as in some other cases.

Changes in the Cerebral Peduncles. In four cases the lesions in the cerebral peduncles were intense, but they were slight in this region in the case of the myoclonic type. The intense infiltration of lymphocytes and plasma cells was not only about the vessels but in the tissue where no vessels could be seen, also in the pia between the crura and especially about the pial vessels, but not in the crura. These escaped almost entirely although the infiltration in the tegmentum came close to the crura. This explains the absence of paralysis of the limbs. The nerve cells near the aqueduct including those of the oculomotor nucleus on each side showed considerable chromatolysis, but little displacement of their nuclei. The cellular infiltration was by no means confined to the area about the aqueduct. Small hemorrhages occurred but were not intense.

In one case a small area, oval and sharply defined from the surrounding tissue, of a light brown color by the Weigert hematoxylin stain, was found just above the innermost part

of the substantia nigra. In a nuclear stain this area was seen to consist of loose glial tissue from which the nerve fibers had disappeared, leaving small holes. This area contained many large cells with large nuclei, probably they were the corps granuleux (fatty granular cells). This area represented the late stage of a focus of inflammation and resembled by its appearance and sharp delimitation in a striking degree one of the sclerotic patches by the Weigert stain in a case of multiple sclerosis. Only one such sclerotic patch was found and in only one case, but its discovery suggested the possibility of multiple sclerosis developing after epidemic encephalitis.

It seems remarkable that only in the case of the myoclonic type little cellular infiltration was found in the cerebral peduncles. It is believed that this condition will be determined in all cases of the myoclonic type. There was some lymphocytic infiltration near the aqueduct but the intense perivascular infiltration of the other cases was absent. The cerebral peduncles were affected in a case of the myoclonic type studied by Winkelman.

Changes in the Pons, Medulla and Cerebellum. The findings in the pons and medulla were similar to those in the cerebral peduncles, and it is noteworthy that they were intense in this region in the case of the myoclonic type, as well as in the others, and much more severe here in the myoclonic case than in the cerebral peduncles. The infiltration was especially intense near the floor of the fourth ventricle, and this probably explains the sudden death with bulbar symptoms so common in this disease, which also occurred in the case of the myoclonic type. The pyramids and pia were little affected. Very little alteration was found in the cerebellum.

Changes in the Spinal Cord. The spinal cord was obtained in two cases only, and unfortunately not in the case of the myoclonic type. In one of the two cases the cervical region was missing. Moderate infiltration of lymphocytes and plasma cells was found in the pia and about the vessels of the

cord substance, and also at some places within the cord without apparent association with a vessel. The nerve cells of the anterior horns did not show any pronounced alteration. In one case there was an extraordinary number of corpora amylacea in the thoracic region, and the patient was not advanced in years.

The noteworthy finding in this study was the slight involvement of the cerebral peduncles in the case of the myoclonic type when the medulla oblongata showed severe cellular infiltration and the basal ganglia also, though less severe than the medulla oblongata. Sudden death occurred in this case. Also the area of degeneration in one case resembling that of multiple sclerosis; the peculiar heaping up of ependymal cells in one case; the escape of the pyramidal tract in all the cases, and the slight implication of the cerebral cortex. In no case were there found extensive hemorrhages such as have been seen in other forms of inflammation of the central nervous system.

The following questions submitted to Dr. Spiller before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TILNEY: In selecting the paracentral lobules, was there any special reason for confining the examination of the cortex to that part of the brain?

DR. SPILLER: No, only that the paracentral lobules are the most satisfactory for routine study and I have always taken them for that purpose. They contain the largest nerve cells of the human body, are the easiest to study, and give us more conclusive evidence as to what the findings may be.

DR. TILNEY: Did the medullary substance show any changes?

DR. SPILLER: No; not anything very significant; the findings were rather insignificant. I do not know any reason why I should not say that it was Dr. Copeland who took a piece of this brain, could not find anything that was very striking, and thought it was not a case of epidemic encephalitis. He told me, and other well known pathologists told me, in another case they found in the kidneys quite sufficient to explain the symptoms, but the lesions

in those two cases in the basal part of the brain were as typical as anyone could wish to see.

DR. TILNEY: Nearly everyone has made some statement in reference to chromatolysis. The degree of chromatolysis seems to be a point of debate.

DR. SPILLER: I think chromatolysis is debatable under all circumstances. When the matter of chromatolysis first came out in the literature of twenty-five or thirty years ago, I remember working in a laboratory and being shown changes in the nerve cells which were gotten in nicotine and strychnine and various forms of intoxication. When you consider the methods of hardening—these were not done immediately after death—one must be extremely cautious in accepting any judgment in regard to these final cell changes. Chromatolysis occurs so very readily. I do not think it is a post-mortem change, but one must not attribute too much to chromatolysis. I did not find in any of these the blowing up of the cells or the marked eccentric position of the nucleus—none of those changes which are so very striking and of so great pathological importance.

DR. TILNEY: With relation to the hemorrhages described, were they entirely extravascular, perivascular or in the Virchow-Robin spaces?

DR. SPILLER: They were around the vessels and in the vessel walls. They were never very numerous or intense in the sections I had an opportunity of studying, and did not get out into the tissue very much.

DR. TILNEY: Did the sclerotic patch described in the cerebral peduncle have many features in common with patches of multiple sclerosis?

DR. SPILLER: It looked exceedingly like multiple sclerosis, and when I examined it with an acid stain which characterized these patches so clearly in multiple sclerosis, I could not have told. Even under a nuclear stain it had the appearance of a sclerotic patch. But we cannot conclude that such a patch is going to proliferate or is going to produce further symptoms. I look upon it as a scar and I would not, therefore, attribute too much to it. If such a patch or such patches are found in other cases, they will have very great significance. There is a possibility that following epidemic encephalitis these patches from areas where there has been intense infiltration may become numerous, and

possibly even the neuroglia may proliferate and we may have, though I have not seen any such cases nor heard of them, a typical picture of disseminated sclerosis resulting from lethargic encephalitis.

DR. TILNEY: Is it your opinion that there is any possible relation of epidemic encephalitis to multiple sclerosis?

DR. SPILLER: I do not know of any relation between them. The subject of multiple sclerosis is now undergoing somewhat of a change in regard to our opinions of it. In the past few years I have reported a case where there was certainly a proliferation of the neuroglia, and I could not believe in a view formerly held that it was merely the replacement of destroyed tissue. It was certainly an active process going on. I could see where these new neuroglia cells like an advancing army were going into the more nearly normal tissue of the brain. In the spinal cord the lesions were more advanced and there was nothing of that. No human being, I venture to say, could have seen in the spinal cord anything differing from any ordinary case of multiple sclerosis; but in the brain it was certainly the neuroglia in the active state. I see no direct connection whatever between multiple sclerosis and epidemic encephalitis.

DR. HUNT: Are there any lesions in the nerve roots to explain the radicular types of the disease?

DR. SPILLER: In regard to the involvement of the root, how can the cervical nerves escape if all about them is infiltrated with cells? They are involved more or less, but I have not had enough cases to study in which the spinal cord was affected. I have not seen sufficient indications in the spinal cord roots to justify any conclusions of decided infiltration of the roots of the spinal cord.

DR. SACHS: It is conceded that there are no large hemorrhages in these cases, but I would like to ask Dr. Spiller whether he would recognize a distinct difference between these cases—this process and the process we formerly acknowledged to be the process of acute hemorrhagic and acute encephalitis?

DR. SPILLER: No, because I think these cases are sometimes spoken of as acute hemorrhagic and acute encephalitic. I reported a number of years ago a case of myoclonic type of poliomyelitis where the hemorrhages in the anterior horns were very numerous, that I should regard as a type of hemorrhagic infiltration, but in these cases the hemorrhages had to be hunted for in order to

be found. They did not strike the eye on first looking at the sections. They were small collections of red blood corpuscles.

DR. TAYLOR: Admitting neuronophagia, is there any fundamental difference then except in degree between this lesion and the lesion of poliomyelitis?

DR. SPILLER: A most interesting subject. I really would be in great doubt if I had a section presented to me. I think sometimes clinically we are in great doubt. I had a patient who came from the coast of Maine at the time there was an outbreak, and I thought it was a case of lethargic encephalitis; later I began to believe it was poliomyelitis of the basic gangliar type. I believe you do not get in the spinal cord the changes in encephalitis that you get in poliomyelitis, and you have a point of distinction. But if you take a section of what you suspect to be a basilar form of poliomyelitis, I do not see how under the microscope you could say positively it was a case of lethargic encephalitis and not poliomyelitis. I myself would not, I am sure.

DR. PATRICK: You say that in the case of acute bulbar paralysis you could not tell it in looking at the section. Could you distinguish it from poliomyelitis?

DR. SPILLER: You would expect to find changes in the spinal cord which are characteristic in the acute cases. In looking merely at the bulbar part, I should not be able to tell it, I am afraid.

DR. TAYLOR: Does it not bring us back to the original idea that encephalitis and poliomyelitis are presumably due to the same cause and are essentially the same lesion with different localizations? It seems we are going back to the original idea. In other words, are we not making again unnecessary distinctions between these lesions which may be essentially the same, simply differing in localization rather than in kind?

DR. SPILLER: There is a great deal in that idea, and yet from investigations of Dr. Strauss and his co-workers there are going to be other means of establishing that the two diseases are not necessarily the same thing simply because the lesions resemble one another. Histologically, they are certainly very close.

DR. PRINCE: In rapid cases what is the common cause of death?

DR. SPILLER: In one case a man came to me who had the myoclonic twitchings and jerking. I thought he was in no particular danger and was probably going to get well. I was startled to hear when I went to the office the next morning that he had died at

five o'clock. I found that his medulla oblongata was the seat of intense infection, and I am inclined to think these sudden deaths are due to the involvement of the medulla oblongata.

DR. PRINCE: What is the common cause in general though in rapid cases?

DR. SPILLER: I should attribute these sudden deaths almost invariably to the oblongata. It is hard to answer that otherwise. The complication is there. In a number of these cases there are serious kidney troubles, and I do not know if it is not from the kidneys. I should not be able to answer that.

DR. LADD: Did you note any difference between the pathology of the venules and arterioles?

DR. SPILLER: That is a point emphasized a great deal by foreign writers. It has been generally acknowledged that the veins are more involved than the arterioles. It is not always easy in a small arteriole to say positively whether it is a vein or arteriole. I have had difficulty in determining that.

CHANGES IN THE ENDOCRINE SYSTEM (HUBERT S. HOWE). Histological examination of the glands of internal secretion in epidemic encephalitis was undertaken to ascertain if any alterations were to be found, and if so whether they had any bearing on the course or manifestations of the disease. The material consists of four cases that were under observation prior to death. The autopsies were made shortly after death. The material was fixed in Zencker's solution and the blocks imbedded in paraffin. Sections were stained with hematoxylin and eosin.

Histological examination was made of the thyroid gland, adrenals, the pituitary body, gonads and pancreas.

THE THYROID GLAND

Case I. The alveoli were of all sizes and filled with colloid. The lining epithelium was cuboidal. There was very little interstitial tissue and in places this appeared hyalinized or even colloid-like. In the interstitial tissue were a few localized collections of small cells with dense pyknotic nuclei. The vessels were greatly congested.

Case II. The thyroid was small, soft and symmetrical, and grossly normal. Microscopical examination showed the vesicles of average and about uniform size, filled with pinkish staining colloid. The cells were cuboidal and for the most part lined the acini in single rows. The blood-vessels were not congested.

Case III. The thyroid was of normal size, and on section showed normal colloid material. Microscopically, the vesicles appeared of average size, filled with a pink-staining homogenous colloid and lined by a single layer of cubical cells. There was no increase in the interstitial tissue and but moderate congestion of the blood-vessels.

Case IV. The thyroid was of normal size. On section there was a slight decrease in the average colloid content. Microscopically, the acini were small and for the greater part lined with a single layer of epithelium. The interstitial tissue was increased and contained areas of hyalinization.

THE ADRENALS

Case I. The capsule was of average thickness. The cells of the cortex were well preserved and normal; the medulla showed moderate congestion.

Case II. The adrenals were equal, small and flat. They contained considerable fat in the cortex with a broad inner zone and a small amount of white medulla. Microscopical examination showed the cortex to contain much lipoid. At the junction of cortex and medulla were several large collections of round cells. In the reticular cortical zone was considerable lipochrome pigment. The medulla was broad, taking the chromaffin stain.

Case III. The adrenals presented a yellow cortex and a deeply stained pigmented inner zone. Microscopically, the glomerular zone was poor in fat, while the glomeruli of the vesicular zone were evacuated. The whole gland was markedly congested.

Case IV. The adrenals, though grossly normal, microscopically showed thickening of the capsule and hyalinization. In the medulla the blood vessels were congested.

THE PITUITARY BODY

Case I. Pars Anterior. The reticular arrangement was not very apparent as the cells were large and entirely filled the acini.

The blood sinuses were dilated and congested throughout the entire lobe except for one area. The cells were predominantly basophilic. Those around the periphery were more intensely so, but even in the center they were more numerous than other types. The cells were polygonal with well defined outlines. The cytoplasm was finely granular. A few contained one or two vacuoles, usually in apposition with the nucleus. The nuclei were generally large, irregularly spherical, with a well defined reticulum in whose meshes were numerous chromatin granules. There were usually two or three large irregular chromatin masses mainly toward the center of the nucleus, and many smaller ones principally at the periphery. In one portion the gland stood out in contrast to the surrounding tissue. While the blood sinuses were congested in other portions, here only a few small capillaries were seen. The connective tissue stroma was swollen, edematous and fragmentary. The cells were of uniform staining and faintly basophilic. They were swollen and poorly outlined with frayed and irregular margins. The cytoplasm was coarsely granular. The nuclei were frequently pyknotic or occasionally swollen with large clear spaces between the chromatin network. In some instances there had been a rupture of the nucleolar membrane and a breaking up of its substance. Here and there were masses of protoplasm without nuclei or cell outlines. This entire area had the appearance of an early stage of coagulation necrosis from deficient blood supply.

Pars Intermedia. The cells were mainly faintly basophilic and arranged in form of large vesicles filled with colloid.

Pars Nervosa. The neuroglial cells appeared normal. Some of the fibers contained a brownish pigment.

Case II. Pars Anterior. The capsule was of normal thickness and throughout the gland the reticular arrangement of connective tissue was well marked. The blood sinuses were moderately dilated. The cells had no definite arrangement but formed irregular groups. Many were shrunken and in the center of the acini, not in apposition with their walls. The central cells were almost entirely eosinophilic, those at the periphery were basophilic. The cells were of average size with well defined outlines and a single deeply stained nucleus in the center. Scattered throughout the anterior lobe were many large eosinophilic cells with a granular cytoplasm. These were more prevalent around the periphery where they frequently were the only cells in an individual acinous space. Throughout the medial

portion of the gland they were rarely seen. The vascular sinuses were dilated. No hemorrhages or thromboses were seen.

Case III. Pars Anterior. The connective tissue stroma appeared normal. The vessels were dilated and congested. The cells were mainly basophilic at the periphery, distinctly acidophilic in the center. Neutrophilic cells were scattered throughout the section but were in the minority. The eosinophilic cells were of average size with finely granular protoplasm containing no vacuoles. The nuclei were spherical and deeply stained. They contained a chromatin network and granules but were opaque. The basophilic cells were smaller than the oxyphilic with less clear and more irregular margins. The cytoplasm was more coarsely granular and contained occasional vacuoles. The nuclei were large and translucent with a chromatin network and granules. Two small vessels were thrombosed with what appeared to be platelet thrombi. Many cells around these vessels were necrotic. In some areas there was an accumulation of loosely granular cytoplasm with no nuclei or remnants, in others the nuclei remained while the cytoplasm was disintegrated. Some nuclei appeared normal, others were fragmented and degenerated.

The *pars intermedia* contained many spaces filled with faintly basophilic colloid.

The *pars posterior* was normal.

Case IV. *Pars anterior* showed marked congestion. Microscopically the reticular stroma was normal. The vascular spaces were dilated and many contained a homogeneous hyaline material. The cell staining reaction was mainly basophilic, but the central cells were mostly neutrophilic with a few scattered oxyphilic. Most of the basophilic cells were large and deeply stained. The cytoplasm was finely granular and rarely contained vacuoles. The margins were ill-defined. The nuclei were large, irregularly spherical or oval, occasionally sausage-shaped or triangular. They contained a well marked chromatin network supporting dense granules. No thromboses or necrotic areas were seen. The juxtoneural epithelium and posterior lobe were missing.

THE GONADS

Case I. The testicles were normal.

Case II. Testicles. The left was soft and congested. The right, also soft and somewhat smaller than the left, was slightly adherent

around the epididymis to the parietal layer of the tunica vaginalis. Microscopically there was no spermatogenesis and practically all of the elements were absent, only the sustentacular cells and debris remaining in most of the tubules. The basement membranes were normal. The interstitial cells contained considerable brown pigment.

Case III. The testicles were apparently normal in the gross. On histological examination spermatogenesis appeared imperfect. Many pyknotic nuclear fragments were seen, with well preserved mitoses and apparently normal spermatids and spermatozoa.

Case IV. The ovaries showed some old and some more recent corpora lutea. Microscopically, there were a few semi-replaced corpora lutea. Otherwise the entire ovary had been replaced with fibrous tissue.

THE PANCREAS

Case I. The pancreas was congested but otherwise grossly normal. Microscopically it was normal except for a few large circular open spaces which may have contained fat. Some had a thin hyaline membrane lining.

Case II. The pancreas was grossly and microscopically normal.

Case III. The pancreas was reddish, with marked congestion of the blood-vessels. The glandular tissue had a glossy, digested appearance. On microscopical examination the acini were decreased in size; the cytoplasm of the cells appeared vacuolated. Only a few of the islands of Langerhans were evident, many being replaced by fibrous tissue. There was increase of interstitial tissue replacing many glands and giving the tissue a fibrous appearance. In areas this connective tissue appeared necrotic. The blood vessels were sclerotic and many were obliterated.

Among the clinical manifestations of the disease which might be interpreted as endocrine disturbances are *profuse sweating, weakness, low blood pressure, menstrual disturbances, impotence and metabolic disorders resulting in increase of weight*. It seems probable that further study will show these disturbances as dependent primarily on lesions in the nervous system, or the direct effect of disease toxins on the individual secretory organs causing altered functions without distinct histological changes.

SUMMARY CONCERNING ENDOCRINE GLANDS

With the exception of the anterior lobe of the pituitary, there were no definite pathological alterations in the glands of internal secretion.

In the pars anterior of the pituitary two kinds of alterations were observed—a predominance of basophilic cells and areas of focal necrosis and capillary thromboses.

The normal histological variations in the anterior lobe of the pituitary are marked and the significance of the preponderance of the various types of cells is little understood.

It seems unlikely that there could be sufficient interference of function in the pituitary body to cause the lethargy of epidemic encephalitis. The focal necroses and capillary thrombi are somewhat similar to the condition found in the liver in typhoid fever and in some cases of sepsis. Here, as in the liver, the collateral circulation is so extensive that it is difficult to believe that capillary thrombi could impair the circulation sufficiently to induce necrosis. It seems more probable that both changes result from the circulating toxins. These necroses were not prominent in the specimens studied and it is doubtful if they were sufficient to cause much alteration in the function of the gland. So that, while the alterations described in the pituitary are definite, there is at present no evidence that they are important or influence the course or manifestations of the disease. To reach definite conclusions concerning the changes in the internal secretory organs in epidemic encephalitis, many more cases must be studied.

The following questions submitted to Dr. Howe before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TILNEY: Were the pineal or chorioidal glands examined in any of the four cases?

DR. HOWE: No, only those I mentioned.

DR. TILNEY: Did the appearance of the medulla of the adrenal suggest any marked departure from the normal?

DR. HOWE: No, the medulla of the adrenal appeared normal. In one case there was an increase in the lymphoid tissue between the medulla and the cortex, but that is normal and we paid no especial attention to it.

DR. TILNEY: In the pituitary body, did you find any disproportion in the basophilic and the acidophilic cells?

DR. HOWE: That, of course, is a difficult point to answer. I have never seen two pituitaries that looked exactly alike in any condition, and while as a rule the oxyphilic cells predominate and the basophilic cells are largely at the outside, in these cases all of them I examined seemed to be in a greater proportion than is usually seen. I do not know that you could say it was abnormal, but I think you would term it unusual in appearance.

DR. TILNEY: Sometimes in inflammatory conditions of the pituitary, there is an invasion of the posterior lobe by aciniform collections of basophilic cells. Did you find anything of this kind in the pars infundibularis?

DR. HOWE: No; that appearance was not found in any of the four cases.

DR. TILNEY: Concerning the residual lumen, did that contain any increase or decrease of colloid substance?

DR. HOWE: All of these cases were adults. I think the youngest was thirty-eight and the oldest fifty-three. I think one was fifty and another fifty-one, and there was considerable colloid, but I think not more than is usual in patients of this age.

DR. TILNEY: Do you consider the thrombosis of the pituitary vessels to be specific of this disease?

DR. HOWE: I do not believe we know enough about the appearance of the pituitary in acute infectious diseases. As a rule the glands are not saved. It is quite likely that this does occur in other acute infectious diseases.

DR. TILNEY: Is it your opinion in these cases you have examined, that the thyroid, adrenals, pituitary, pancreatic and other endocrine elements play no very important part in the symptoms or pathological appearance of the epidemic encephalitis?

DR. HOWE: I think all that you can say in answer to that point is that if there are alterations they are largely functional rather than histological, and that you cannot determine by a study of this kind, because the glands really appear quite normal except for some minor changes.

DR. TIMME: Did I understand you to say that the patient showing pituitary thrombus had lethargy as a symptom?

DR. HOWE: Yes; the patient with the thrombi had a period of lethargy about three weeks before he died.

DR. TIMME: Do you know the immediate cause of death?

DR. HOWE: In the second case I am sure it was due to respiratory paralysis.

DR. TAYLOR: You would not say there was anything specific in any of these lesions, and would call this research therefore negative?

DR. HOWE: I have never seen thrombi in the anterior lobe of the pituitary in any other condition, and I have never seen it described in the literature. But I do not think we know enough about it as yet.

DR. TAYLOR: Has Dr. Howe seen cases with great increase in weight?

DR. HOWE: Yes, I have. I remember one patient very distinctly, a young girl of fourteen who had acute encephalitis with a Parkinsonian residuum, and her greatest weight before was 107 pounds. In six months after this period she gained so as to weigh 149. I have seen one or two others of marked increase in weight. But I have not been able to study that patient thoroughly yet, and do not know whether she presents any other pituitary signs. I know that menstruation came on during her first illness and has proceeded regularly ever since. The only cases of impotence that I have seen have been in patients having the paralysis agitans type. I have seen that occur several times.

DR. TIMME: Have you seen any cases in which there has been marked pigmentation to the extent of bronzing the entire body?

DR. HOWE: No, I have not.

LESIONS OUTSIDE OF THE CENTRAL NERVOUS SYSTEM (WILLIAM BOYD). It would appear that encephalitis lethargica must be regarded as a general infection with special localization in the central nervous system. It is possible, however, that in many cases such localization never takes place, and that the patient suffers merely from some mild febrile disturbance the nature of which is never recognized.

Changes in the Serous Membranes. Petechial hemorrhages in the serous membranes identical with those found in conditions of septicemia occasionally occur. In three cases in a series of sixteen autopsies widespread petechial hemorrhages were observed scattered over the epicardium, the pleura on both sides, the peritoneum and both surfaces of the diaphragm. The condition was so striking as to suggest at once the possibility of a septicemia, but the brain findings were those characteristic of encephalitis lethargica. In two other cases there were small hemorrhages under the endocardium.

Microscopic Changes in the Kidneys. The kidney was examined in eight cases and in every instance showed changes which appeared to be distinctly pathological. The kidney lesions were of two main types, vascular and tubular.

The vascular changes consisted in intense congestion of the capillaries. This was most marked in the straight vessels of the medulla, many of which were so distended as to produce narrowing of the lumen of the collecting tubes. In places hemorrhage had occurred from these distended vessels into the tubules. Occasionally the vascularity in the medulla was so great as to suggest the edge of an infarct. Both the glomeruli and the intertubular plexus showed a moderate degree of congestion, and a few red blood cells could be seen in the capsular space of some of the glomeruli. The above description is that of a severe example of the condition, but minor degrees of intensity were constantly present. The tubular lesions were degenerative in character, and resembled those of the nephrosis described by Volhard and Fahr, or the tubular nephritis produced by such an irritant as corrosive sublimate.

The cells to suffer most were those of the convoluted tubules and the ascending limb of Henle. In every case there was a marked degree of cloudy swelling, and in a few instances the nuclei had disappeared and the cells were completely disintegrated. The contrast between the con-

volute and the collecting tubules in the more marked cases was striking in the extreme.

It must not be thought, however, that the collecting tubules escaped entirely in every instance. In several cases the lining cells were crowded with yellow granules. As these were most abundant in areas where hemorrhage had occurred, it is probable that they were of the nature of blood pigment. In one case the cells of the collecting tubules contained granules which gave a fat reaction with Scarlet R in frozen sections. The convoluted tubules in this case, although profoundly degenerated, gave no fat reaction.

An additional lesion was observed in one of the cases with widespread petechial hemorrhages in the serous membranes. Most marked in the boundary zone between the cortex and the medulla although to a lesser extent elsewhere throughout the cortex, there were found collections of small round cells with a few polymorphonuclear cells. These strongly suggested a focal infection, and the appearance was not unlike that of a suppurative nephritis.

Appearance of Homogeneous Hyaline Bodies in the Central Nervous System. A change worthy of note was the presence of numerous spherical, homogeneous hyaline bodies, resembling the corpora amylacea found in the prostate and other organs. These bodies were found in severe cases, in the young as well as the elderly. As a rule they were of uniform size, but occasionally showed variations in diameter. The center was darker than the periphery, but there was no definite nucleus. Concentric striations could be made out in many instances. In one case they were present in the cerebrum, basal ganglia, midbrain, pons, medulla and cord, but not in the cerebellum. Although present in both gray and white matter throughout the brain and cord, they were most numerous at the surface, around the aqueduct of Sylvius, and under the floor of the fourth ventricle.

The bodies stained blue with thionin, pale blue with hematoxylin, blue-black with iodine, but not at all with van Gieson. They are probably products of degeneration, similar

to the colloid bodies found in old age. They appear to be due to neuroglial degeneration. They are certainly not derived from ganglion cells, for they are as numerous in the white as in the gray matter.

LESIONS IN THE BRAIN PRODUCED BY LEAD AND OTHER POISONS CONTRASTED WITH THOSE OF EPIDEMIC ENCEPHALITIS (GEORGE B. HASSIN). Non-suppurative inflammations of the brain generally termed encephalitis may be caused by infections or intoxications. The infectious group is mainly represented by general paralysis and epidemic encephalitis; the toxic group by intoxications such as lead or arsenic. In both these large groups of non-suppurative inflammation of the brain there are to be found parenchymatous (or better, ectodermic) and interstitial (or mesodermic) changes.

Ectodermal Changes Contrasted. The ectodermic changes, that is to say, those of the neuroglia and ganglion cells, do not exhibit any specific pathologic features, being practically alike in the epidemic and the lead varieties of encephalitis. In both forms there is present an excessive number of glia nuclei, which may be somewhat increased in size and possess a visible rim of cytoplasm. However, in both large protoplasmic glia cells, myeloclasts, myelophages as well as various types of gitter cells are absent. As to the changes in ganglion cells and nerve fibers, the former are represented by chromatolysis, neuronophagia, satellitosis, and accumulation of fat-like substances. In short, the parenchymatous changes are degenerative in character.

Mesodermic Changes Contrasted. Of much greater significance are the mesodermic changes to be found in the vessels and the pia-arachnoid. In epidemic encephalitis, the vessels are much infiltrated, chiefly with lymphocytes and plasma cells, the infiltration frequently transgressing the perivascular spaces and invading the parenchyma itself. The latter is frequently covered with dense foci of hematogenous elements, mixed with many glia cells, totally obscuring the parenchyma. Such dense infiltrations do not occur in lead

encephalitis. Here the vascular changes are mainly represented by proliferative phenomena. Thus, there may be hypertrophy of the endothelial cells of the capillaries with an abundance of intensely stained protoplasm; there may be proliferated and hypertrophied fibroblasts; there may be an abundance of new-formed capillaries in the shape of buddings or off-shoots; the vessel walls may be thickened, etc. In short, all the various stages or phases of proliferation or new formation of capillaries may be encountered in toxic encephalitis, but not in the epidemic variety.

The vascular changes in the epidemic form are confined principally, though not exclusively, to the midbrain, while in the toxic variety the changes above described are almost universal. They affect every portion of the cerebrum and cerebellum including the pia-arachnoid and its spaces.

The latter structures show particularly noteworthy changes. In lethargic encephalitis they consist of mild infiltration with lymphocytes and plasma cells while in lead encephalitis, especially in early stages, the cell infiltration is much more marked, in fact may be enormous, always combined with great wealth of vessels, both pre- and new-formed. The pial infiltration elements, in lead encephalitis are more numerous, the mesothelial cells, polyblasts and fibroblasts being especially conspicuous. There are also many other elements mostly ill-defined and frequently packed with pigment granules. Such conditions ultimately lead to a general hyperplastic state of the pia-arachnoid, especially on the base of the brain, in the region of the optic chiasm and around the cerebellum.

The prevalence of proliferative mesodermal changes fully justifies the name "*productive*" encephalitis which Bonfiglio proposed for such conditions, while the infectious variety should be termed "*infiltrative*" encephalitis. However marked and important the vascular changes in the cerebral substance, those of the pia-arachnoid and the sub-arachnoid space are of greater significance. Special attention should be paid to these structures in pathologic studies of

typical and atypical brain lesions, for they may reveal changes even when the brain tissue proper appears normal.

The following questions submitted to Dr. Hassin before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TAYLOR: Would you consider it possible that changes you describe as distinguishing the toxic encephalitis from the epidemic might be due to the time element? Would it be possible that if the encephalitic process could be studied, for example, years after, we might find proliferation of vessels? Do you think, in other words, there is a specific difference?

DR. HASSIN: It is absolutely specific in the cases I studied. I had three; two were chronic cases of ten months duration, and these pictures are taken from an acute case of five weeks duration.

DR. TILNEY: In your Case 3 you state that only the productive changes occur in the more chronic cases of lead encephalitis. Would you consider it necessary to take into account the possibility of the influence of time here?

DR. HASSIN: In pial acute cases there are only proliferic changes. The "productive" type of encephalitis is typical for brain lesions caused by lead poisoning.

DR. TAYLOR: Were your lead poisoning sections taken from animals, experimental matter or fatal cases?

DR. HASSIN: From fatal human cases.

CONCLUSIONS OF THE COMMISSION

MATERIAL. It is the opinion of the Commission that while much knowledge has been gained from the pathological material already obtained, the number of cases subjected to autopsy up to this time is nevertheless too small to permit of any final deductions concerning the pathology of epidemic encephalitis. Furthermore, the Commission feels that the pathological material thus far investigated has not been studied with sufficient thoroughness to permit of more than an outline or sketch of the entire pathological process of the disease at the present juncture. This is especially true of the

cerebral cortex and for that matter of the brain stem and spinal cord. Intensive studies by means of appropriate differential stains upon specimens treated in serial sections will afford the most reliable basis from which to draw definitive conclusions.

The investigations of lesions in parts other than the nervous system and particularly in the endocrine organs likewise comprise studies upon cases much too limited in number to warrant ultimate deductions.

The contrasts between the histological changes due to epidemic encephalitis and histological changes caused by other inflammatory toxogenic factors, although appearing in some instances to be well defined, are not yet sufficiently established to warrant a statement that there is a complete specificity in the pathological process of epidemic encephalitis.

The total number of cases up to December, 1920, in which there have been necropsy observations is 113. For purposes of histological comparison and topographical orientation, not more than 50 of these cases are available. No single case has been examined with the completeness of technical detail or anatomical comprehensiveness entirely satisfactory from the pathological standpoint.

The results of experimental pathology, although of much interest and very suggestive, are yet too meagre to contribute measurably to the conception of the morbid process of the disease.

GROSS PATHOLOGY. Upon inspection the dura mater has shown no constant lesion. The pia-arachnoid is often edematous but quite as often shows no pathological changes. The surface of the brain is congested, sometimes intensely so. Free blood may be seen in the sulci but massive pial hemorrhage is rare. The convolutions may be somewhat flattened. The lesions are most intense in the midbrain, pons and medulla, least in the cerebellum. The ventricles are usually normal in size and appearance and contain cerebrospinal fluid of normal appearance. The ependyma,

usually smooth and glistening, is occasionally slightly roughened. The meninges and surface of the spinal cord in many cases resemble the cerebral meninges and surfaces.

MICROSCOPIC CHANGES IN THE CENTRAL NERVOUS SYSTEM. Histologically the essential changes in the brain and spinal cord are:

a. Cellular infiltration chiefly affecting the small veins and, to a less extent, the larger veins, arteries and capillaries. The infiltrating cells are small and large mononuclear lymphocytes and plasma cells. The infiltration is largely confined to the Virchow-Robin and perivascular spaces. It has its greatest intensity in the gray matter of the basal ganglia, midbrain, pons, medulla and spinal cord. The white matter is not entirely immune.

b. Hemorrhage which is usually microscopic and confined to the perivascular spaces of His is also a prominent feature. There is an almost complete absence of thrombosis, and if hemorrhage occurs into the brain substance it is accompanied by a reaction of the surrounding glia. In some cases spherical, homogeneous, hyaline bodies resembling corpora amylacea appear in the affected areas of the central nervous system.

c. Cellular Changes. The nerve cells and their fibers show relatively little evidence of degenerative change in proportion to the severity of the pathological lesion. In areas of the most intense changes the nerve cells often manifest some degree of cloudy swelling, chromatolysis, disintegration of the neurofibrils, satellitosis and neuronophagia. The *neuroglial cells* show marked proliferation in areas characterized by pronounced changes in the nerve cells or in the more intensely hemorrhagic foci.

MICROSCOPIC CHANGE IN THE MENINGES. The pia-arachnoid may be normal. Usually the pial vessels are engorged. The pial layers may be separated and the pial reticulum distended with numerous red corpuscles and mononuclear cells in the interstices. In the sulci intrapial extravasations frequently occur.

MICROSCOPIC CHANGES IN THE NERVE ROOTS AND DORSAL ROOT GANGLIA. In some cases the cranial nerves have been found to be the seat of a perivascular lymphocytic infiltration and an interstitial infiltration of the nerve fibers by lymphocytes. Evidence is still lacking concerning the involvement of the spinal nerves, nerve roots and dorsal root ganglia.

FUNDAMENTAL MICROSCOPIC CHANGES IN ACUTE CASES. The essential histological alteration in all acute cases almost universally appears to involve primarily the mesodermal structures with infiltration of the walls of the smaller vessels and the perivascular lymph spaces with lymphocytes, plasma and large mononuclear cells.

MICROSCOPIC CHANGES IN CASES OF LONG DURATION. Chronic cases usually differ histologically from acute cases. After a duration of several months the vessel walls thicken and frequently contain calcareous plaques. The lumina are frequently closed by fibrous or fibrinous occlusions. Perivascular infiltration is still present and neuroglial proliferation is more pronounced.

MICROSCOPIC CHANGES IN THE ENDOCRINE ORGANS. The only alteration which may be of pathological moment in the endocrine system is the occurrence of focal necrosis, capillary thrombosis and a predominance of basophilic cells in the pars anterior of the pituitary body. This was observed in two cases only. The thyroid, adrenals, pancreas and gonads (testes and ovaries) were found normal in all the cases examined. The Commission is not disposed to attach much importance to the pathological changes in the pituitary body and feels that altogether too few cases have yet been examined with reference to the histological state of the endocrine organs to make any statement regarding the pathology of these organs in epidemic encephalitis tenable. The most that may be vouchsafed is that from limited findings the evidence of pathological alteration seems almost negligible.

Reports on the condition of the pineal and chorioidal glands are thus far not forthcoming.

LESIONS OUTSIDE OF THE NERVOUS SYSTEM. *a.* The *serous membranes* have been found to be affected by changes resembling the conditions of septicemia. Petechial hemorrhages have been observed in the epicardium, pleura, peritoneum and both surfaces of the diaphragm. In several cases small hemorrhages were found under the endocardium.

b. The *kidney* was also found to present pathological changes which were vascular and tubular. The vascular changes consisted of intense capillary congestion with scattered hemorrhages. The tubular lesions were degenerative in character, resembling those of nephrosis described by Volhard and Fahr, i. e., the tubular nephritis produced by such an irritant as corrosive sublimate.

LESIONS OF EPIDEMIC ENCEPHALITIS CONTRASTED WITH THOSE PRODUCED BY LEAD AND OTHER POISONS. It is noteworthy that while ectodermal changes are very similar in lead encephalitis and epidemic, the mesodermal changes in these conditions are quite different. In epidemic encephalitis the vessels are much infiltrated, this infiltration frequently invading the perivascular spaces and the parenchyma. This degree infiltration does not occur in lead encephalitis, which shows mainly proliferation of the endothelial cells of the capillaries and thickening of the vessel walls. The vascular changes in epidemic encephalitis are more closely confined to the midbrain; whereas in lead encephalitis the changes are almost universal throughout the brain.

CHAPTER VII

BACTERIOLOGY AND ANIMAL EXPERIMENTATION; FURTHER STUDIES IN PATHOGENESIS, IMMUNOLOGY AND PHYSIOLOGICAL FUNCTIONING

THE material presented in this chapter consists of reports of various contributors, namely, additional reports by Drs. Leo Loewe and Israel Strauss of the Laboratory of Mt. Sinai Hospital, New York City; of further remarks by Dr. William Thalhimer of Milwaukee; of the report of immunological distinctions of encephalitis and poliomyelitis by Dr. Harold L. Amoss of the Rockefeller Institute; of immunological studies by Drs. Marcus Neustaedter, John H. Larkin, and E. J. Banzhaf of New York; and finally of certain physiological interpretations of the function of the nervous system in respect to those diseases by Professor Frank H. Pike of the College of Physicians and Surgeons, New York City.

CULTIVATION OF THE VIRUS (LEO LOEWE). Early in the work it became evident to Loewe and Strauss that the virus of the disease resides in the nasopharynx. The filtrate of a profuse nasal discharge from a patient was injected subdurally into a monkey. Paralysis of both hind legs followed in seven days and cleared up in two weeks. Lumbar puncture revealed increase in cells,—up to thirty-five lymphocytes per cubic millimeter. This monkey was subsequently shown to have acquired an immunity. Further investigations were carried out along this line with human nasopharyngeal washings. It was also found experimentally that the virus is excreted through the nasopharynx. The inoculation intracranially into rabbits of filtrates of nasopharyngeal washings has become a method of diagnosis. As noted on the chart it

is a method which has given a positive result in 16 out of 21 cases, or 77 per cent. There are cases of encephalitis which do not present the classical symptoms of the disease, and it is in such cases that rabbit inoculation has been especially valuable. The test was positive in one case of relapse. Results seem to point rather conclusively to the nasopharynx as the portal of entry of the infection.

Inoculation of spinal fluids into monkeys and rabbits has demonstrated that the virus is present in the fluid especially in those cases which show an increase in cells. The inoculation of spinal fluid into rabbits for diagnosis in conjunction with the nasal washing method has been employed. Sixty rabbits were so injected with spinal fluids from 28 cases. Lesions were produced in 23 animals, thus establishing the diagnosis in 17 of the 28 cases, or 60 per cent.

To control this work nine nasal washings and twelve spinal fluids from various neurological, medical and surgical cases, preferably surgical, to rule out the possibility of contact infection, were inoculated. The results were entirely negative. Two of the control spinal fluids were from poliomyelitis cases. Three of the nasal washings were from influenza cases.

That the disease is at times a general infection is attested to by our positive inoculations with blood.

In establishing a diagnosis of encephalitis in animals we have been guided by symptomatology, the pathological picture and cultural studies. The histological and cultural studies have been of most value. The lesions in experimental animals are similar both in degree and localization to the well-recognized lesions in the human cases. Throughout our extensive animal experimentation we have never met the spontaneous production of the characteristic lesions. We have resorted to the intravenous inoculation of both virus and culture in several instances in order to demonstrate a selective affinity of the virus and culture for the central nervous system. One experiment is particularly striking. In attempting to obtain a specific serum in the sheep a number of intravenous injections with killed cultures were

given and then a fairly large dose of a virulent culture was injected. After a period of four weeks the sheep developed symptoms of a meningo-encephalitis, to which it succumbed in eight days. Spinal puncture showed eighty-five lympho-

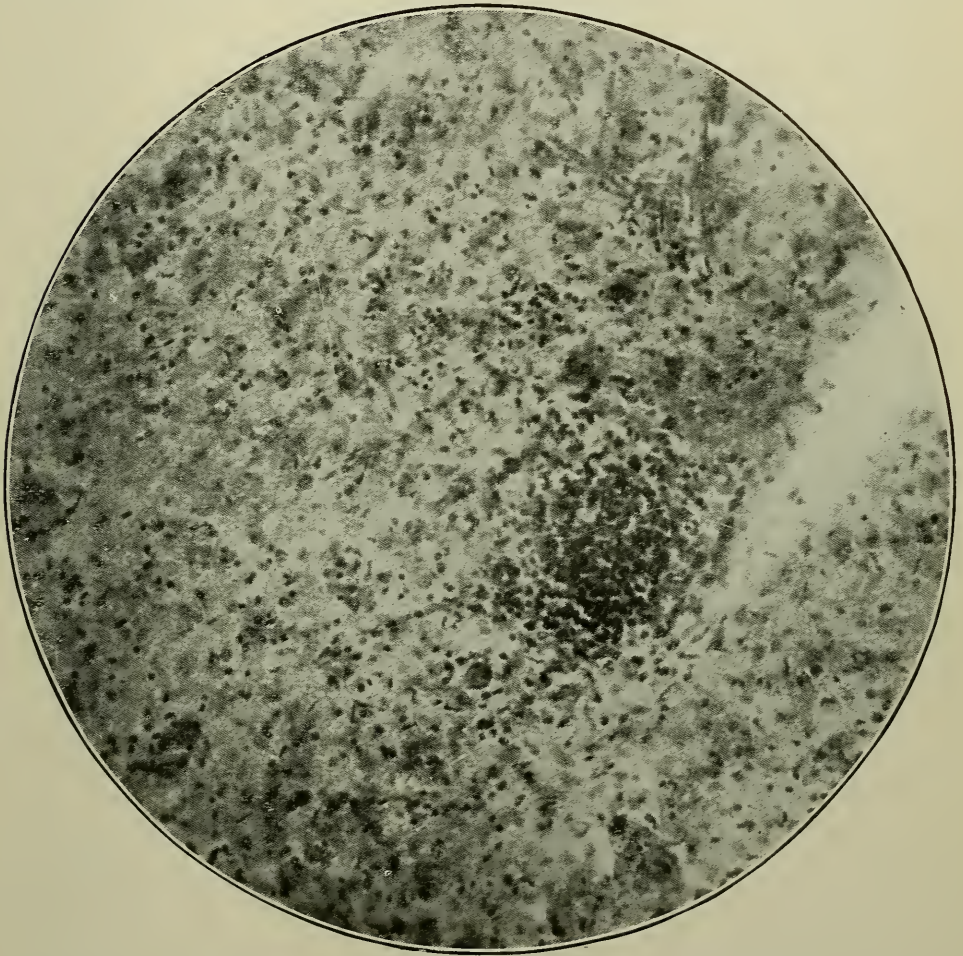


FIG. 20. Human brain. Focal infiltrations with mononuclear cells in the putamen (lenticular nucleus).

cytes per cubic millimeter. An intense encephalitis was present. The other organs showed no abnormalities. The classical picture was produced in a series of rabbits by means of intracranial and intravenous inoculation with saline emulsions and Berkefeld filtrates of this brain. The organism

was recovered from the original sheep brain and from several of the rabbits of the series. These experiments are being prosecuted for subsequent publication.

The materials, after preliminary cultivation on the usual

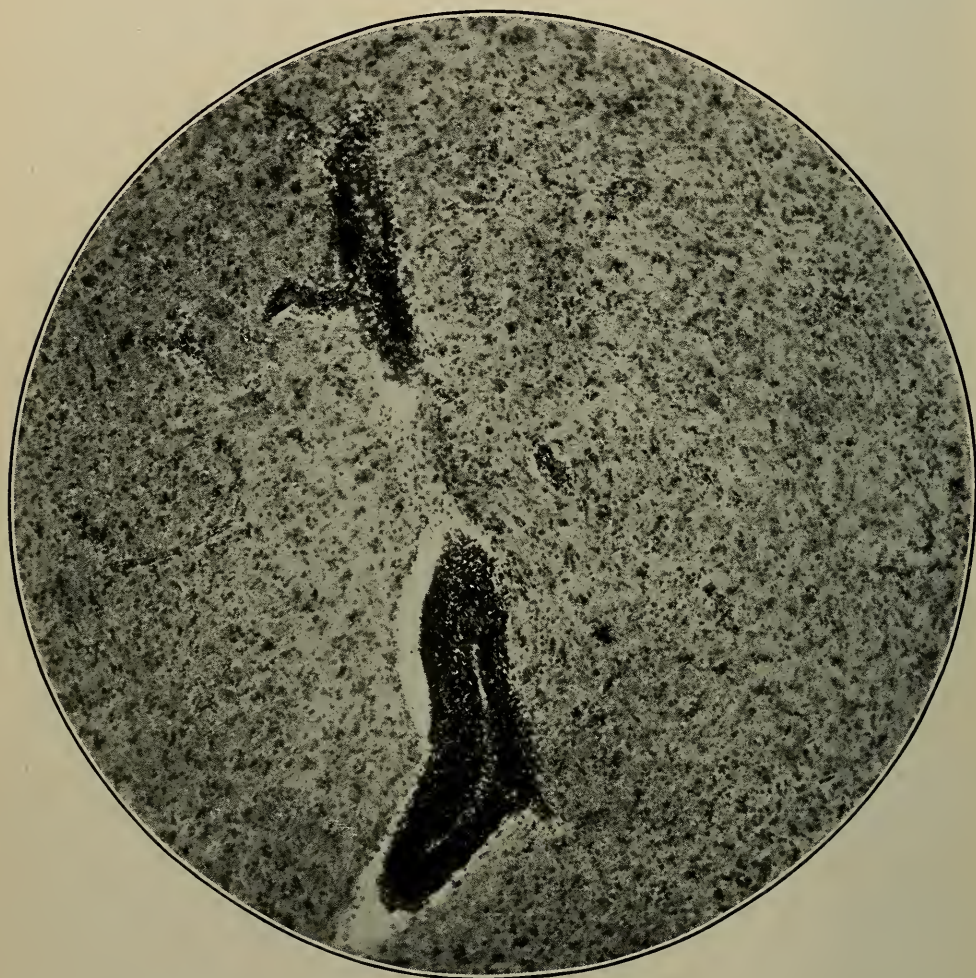


FIG. 21. Human brain. Mononuclear cell infiltration in the Virchow-Robin and perivascular spaces of vessel in the tegmentum of the midbrain.

media to rule out contaminants, were put in the tissue-ascitis fluid medium, perfected by Noguchi. Anaerobic conditions were assured by the use of kidney tissue, by sealing with petrolatum, and later by the addition of glucose. It should be emphasized that the secret of success in this

method is the use of a suitable ascitic fluid. The organism is a minute filtrable Gram-positive coccus appearing in diploforms, chains and clumps. It stains best by prolonged contract with methylene blue, Giemsa or polychrome methylene

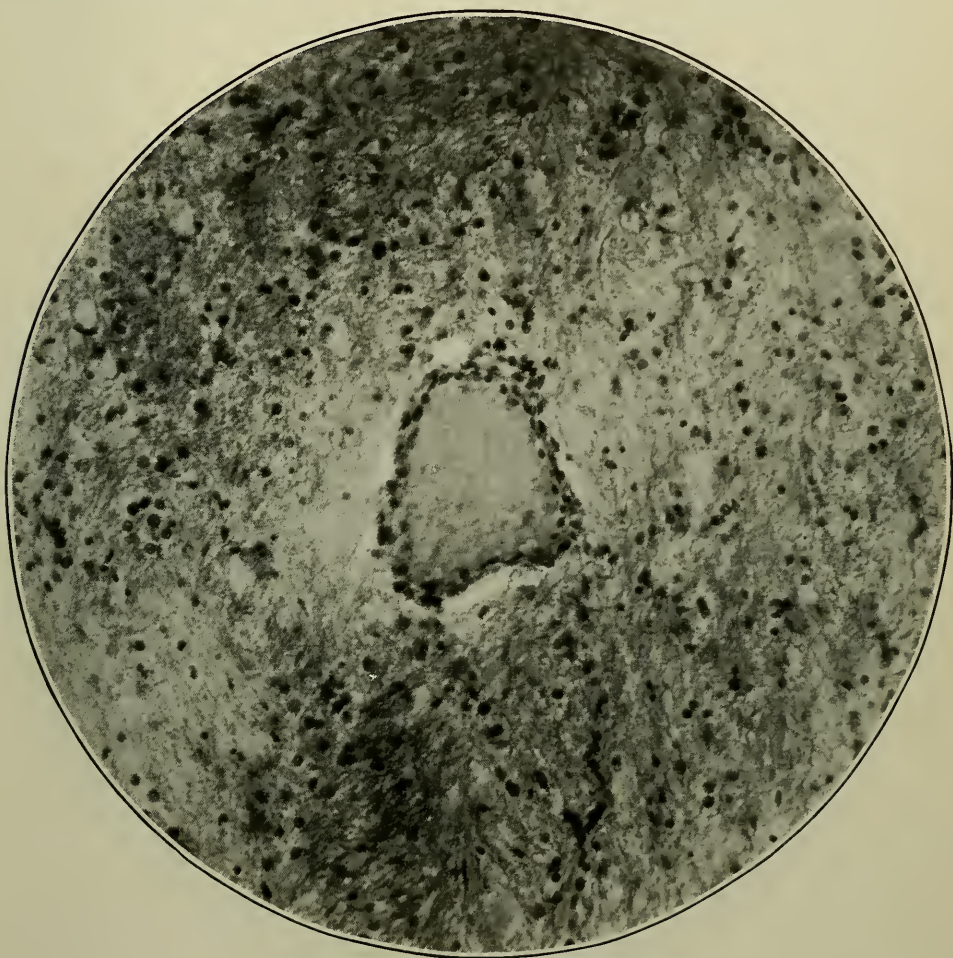


FIG. 22. Monkey brain. Edema, necrosis and adventitial infiltration of vessel in cortex. Animal injected intracerebrally with emulsion of brain of monkey successfully inoculated with infected human brain (Loewe and Strauss).

blue. Morphologically and culturally, the organism found by us resembles that found by Flexner and Noguchi in poliomyelitis.

The organism has been isolated in pure culture from the following materials.

1. Human nasopharyngeal mucous membrane removed at necropsy. The organism has been recovered in pure culture from Berkefeld filtrate of nasopharyngeal mucous membranes from 8 fatal cases of epidemic encephalitis. Out of eleven



FIG. 23. Monkey brain. Cortex showing perivascular infiltration of mononuclear cells. Animal same as that pictured in Fig. 22 (Loewe and Strauss).

attempts, eight or, 73 per cent have been successful. The organisms have been carried as far as sixteen generations in artificial cultures without animal passage. The later strains proved pathogenic for animals. Control cultures of filtrates

of nasopharyngeal mucous membranes of seven patients dying of other conditions have all been sterile.

2. Berkefeld filtrates of human nasopharyngeal washings of 23 cases, typical and atypical, were cultivated with positive

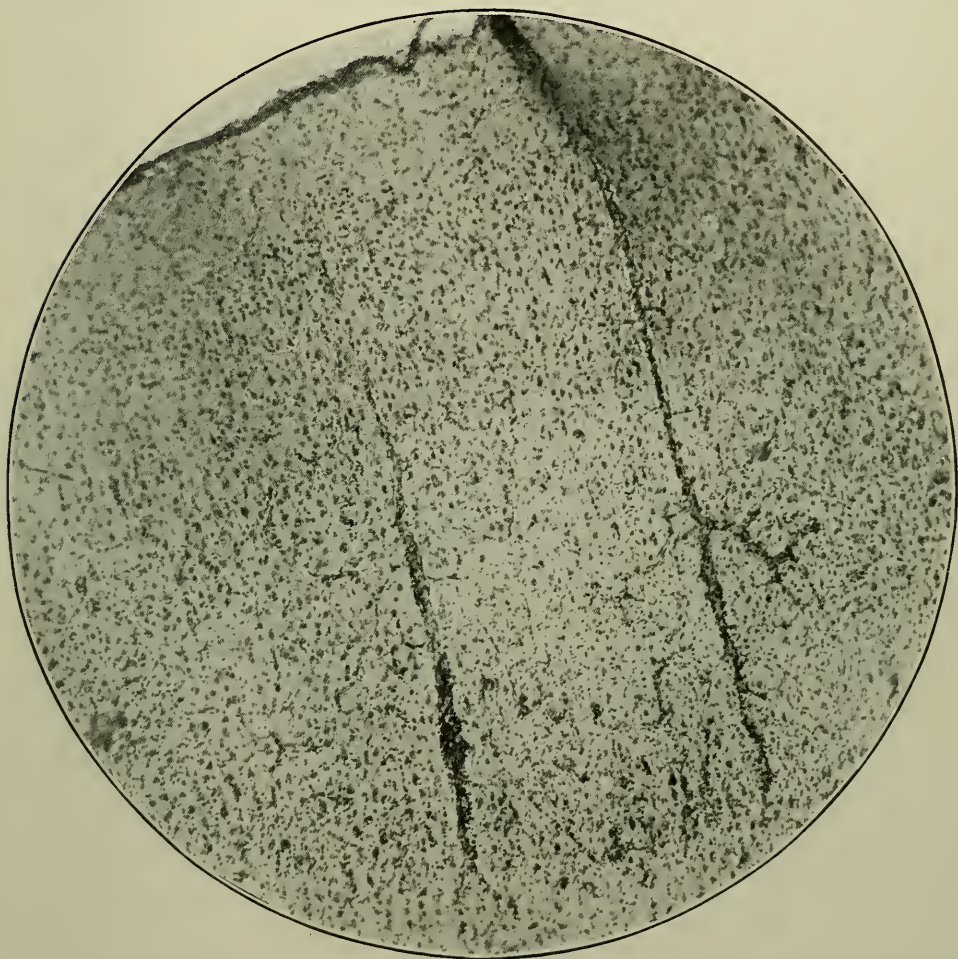


FIG. 24. Monkey brain. Cortex showing perivascular infiltration with mononuclear cells. Animal same as that pictured in Fig. 22 (Loewe and Strauss).

findings in 15 cases, or 66 per cent. Many of these strains were subcultivated successfully and carried along for several generations. The later generations of these cultures again were pathogenic for animals. Control studies were negative in 9 cases—mastoiditis, sinusitis, cholelithiasis, etc.

3. Filtrates of rabbit nasopharyngeal mucous membrane yielded the organism in 3 cases. The rabbits were injected with both filtrate and culture. The organism was recovered also from the brains of animals injected with filtrate of these

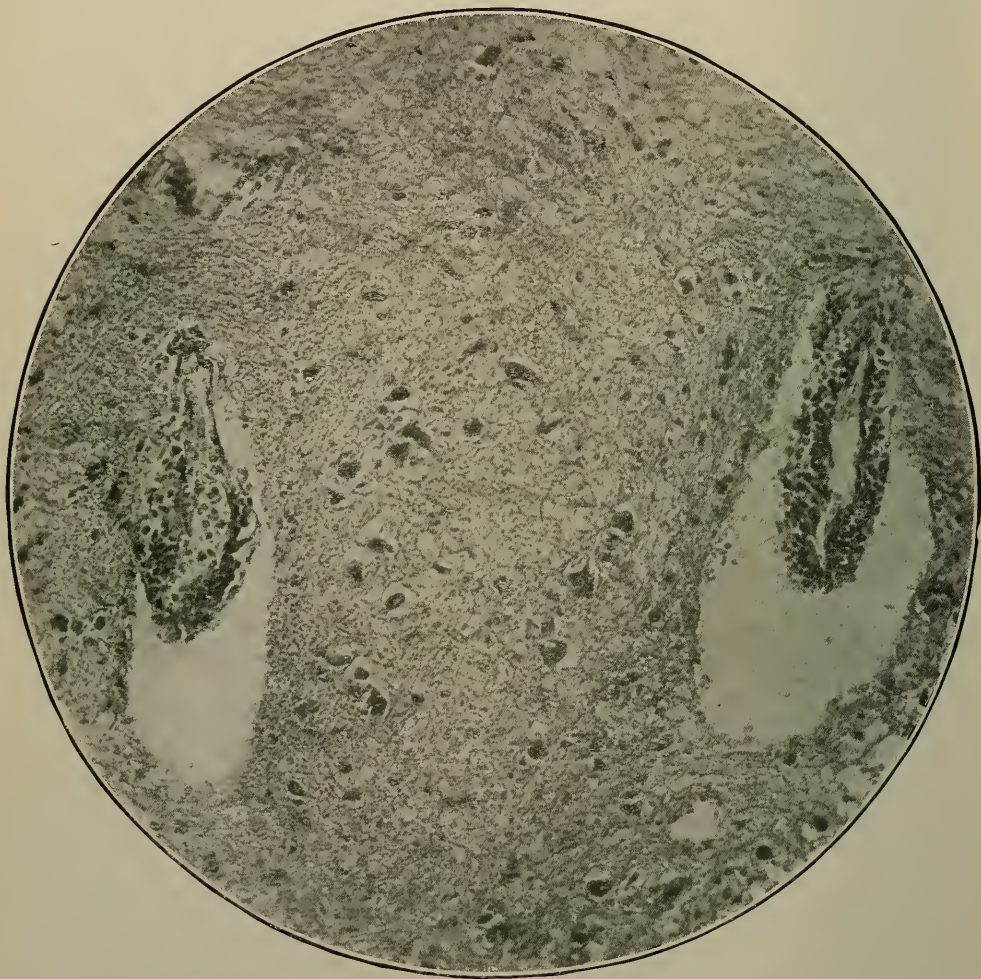


FIG. 25. Monkey brain. Mononuclear cell infiltration in Virchow-Robin space (adventitia). Pons. Animal inoculated with emulsion of brain from a human case (Loewe and Strauss).

nasopharyngeal mucous membranes and also from the brains of animals injected with the organism derived from these rabbit mucous membranes. Cultures of filtrates from seven normal rabbit mucous membranes were negative.

4. Cerebrospinal fluids have been cultured in 28 cases with fourteen positive results. The strains were carried as far as the eighth generation in order to prove their pathogenicity. Control spinal fluid cultures were negative in 12 cases. Two



FIG. 26. Rabbit brain. Mononuclear cell infiltration in the meninges of the cerebrum. Animal injected with Berkefeld filtrate of nasopharyngeal mucous membrane from a fatal human case (Loewe and Strauss).

of these control spinal fluids were from poliomyelitic animal inoculations and cultures were made in most cases immediately after withdrawal of the fluid.

Rabbit Brains. A total of one hundred and twenty-four

rabbit brains were cultivated, using Berkefeld filtrates of brain, blocks of brain and emulsions of brain. There were seventy-nine positives, or 64 per cent. There was one series of seven animal transmissions initiated by a Berkefeld



FIG. 27. Rabbit brain. Perivascular infiltration (principally mononuclear cells) of vessels in the midbrain. Third transmission in rabbit of virus originally derived from human nasopharyngeal mucous membrane (Loewe and Strauss).

filtrate of a human nasopharyngeal mucous membrane. The organism was recovered following each transmission. One of the organisms recovered from this series was injected into animals in the fourth, fifth, sixth, seventh, and eighth

generations, and was recultivated from 50 per cent of the brains so inoculated. In a series of transmissions initiated by spinal fluid from a case of encephalitis, the organism was recovered from the brain in each of the transmissions, the

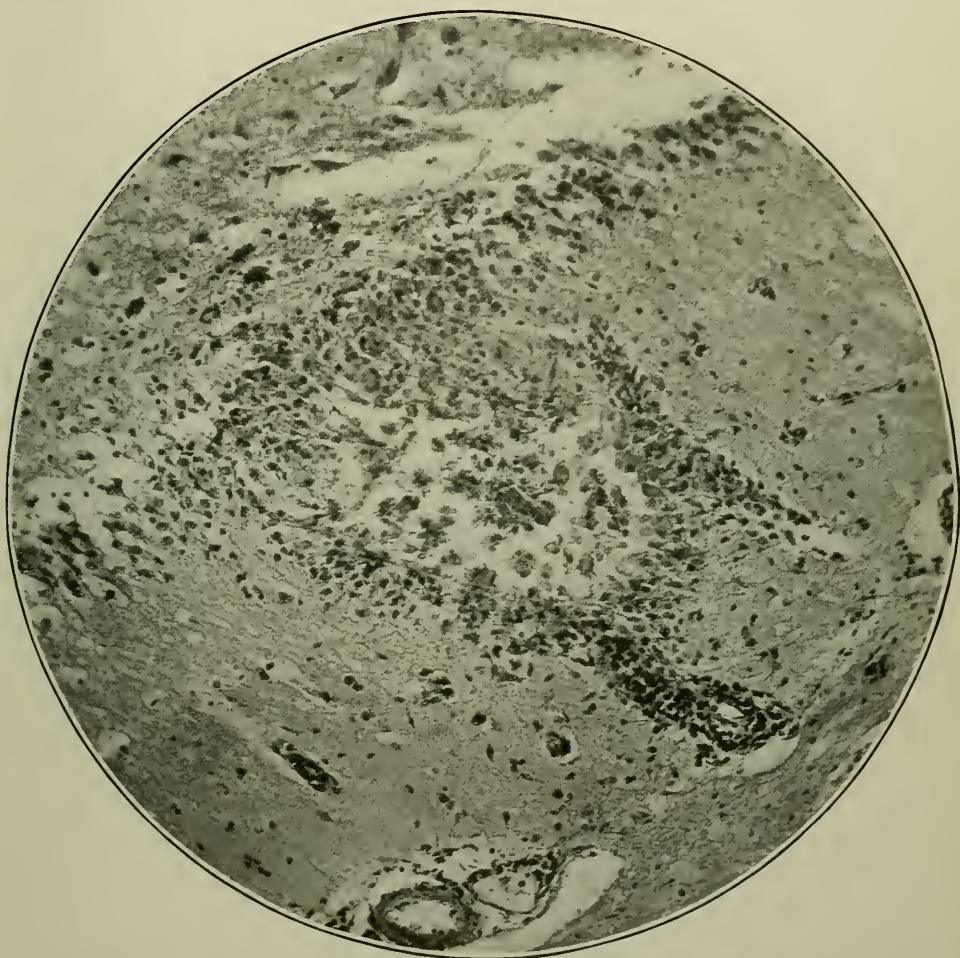


FIG. 28. Rabbit brain. Area of focal necrosis in proximity to vessels showing the perivascular infiltration. Midbrain. Fourth transmission in rabbit of virus derived from human nasopharyngeal mucous membrane (Loewe and Strauss).

positive results making a total of five of the eight brains cultivated.

Monkey Brains. Cultures were made of six monkey brains injected with virus of various kinds (filtrates of human

nasopharyngeal mucous membrane, and of infected nervous tissue from rabbit, monkey and human) and five positive results were obtained.

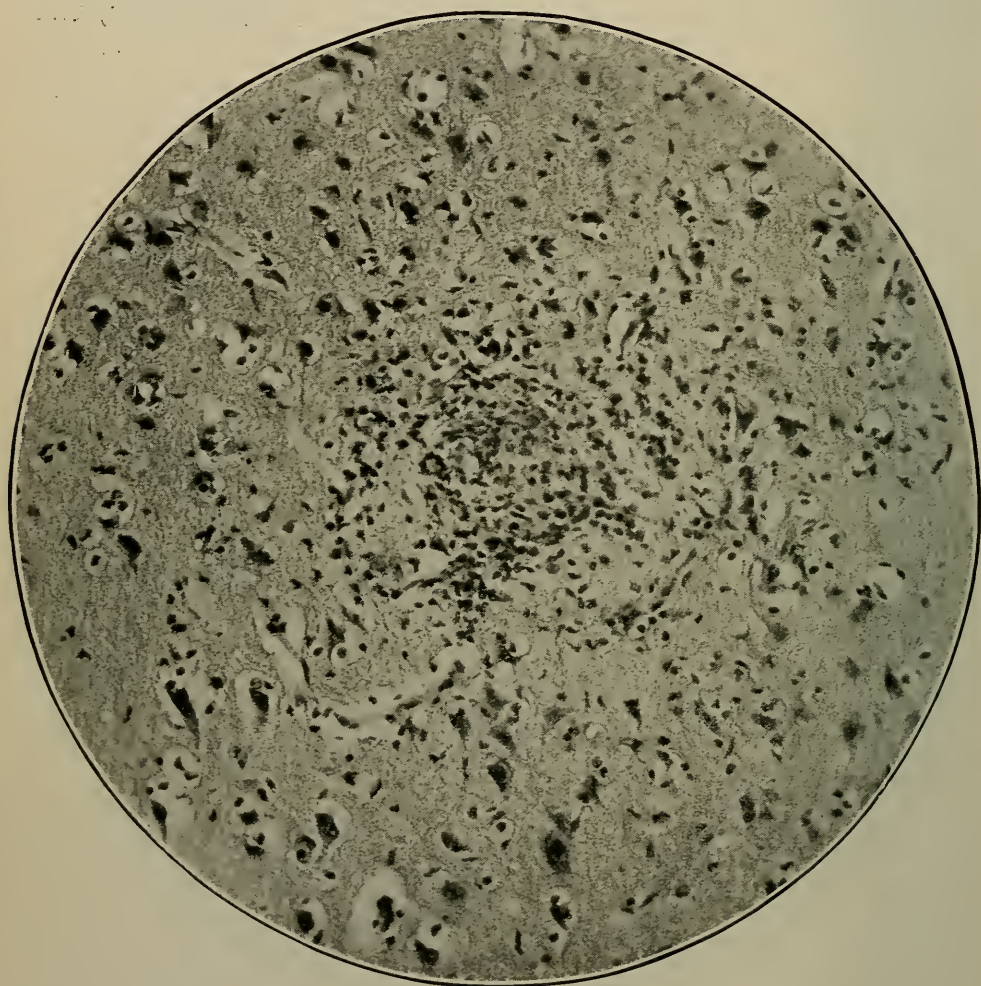


FIG. 29. Rabbit brain. Area of focal infiltration with mononuclear cells in the basilar ganglia. Animal injected with Berkefeld filtrate of brain of monkey successfully inoculated with virus derived from human nasopharyngeal mucous membrane, and which had been transmitted through four generations in rabbits (Loewe and Strauss).

Human Brains. The organisms have been obtained in pure culture from eight brains. Their results have shown that the organism is more readily recovered from the brains of those cases that run a rapid course. They have demonstrated

that there may be a general invasion of the blood-stream in both humans and animals.

As in the case of the virus, monkeys are apparently refractory to cultures of the organisms. The cultures have



FIG. 30. Rabbit brain. Area of midbrain showing perivascular infiltration with round cells. Same animal as Fig. 29 (Loewe and Strauss).

proved pathogenic for both rabbits and monkeys in the later generations. This would tend to rule out the possibility that original virus carried over in transplants is responsible for the potency of their cultures. This fact was proved by a number of dilution experiments described in the *Journal*

COMPLETE DATA ANIMAL INOCULATIONS

No. Cases	Inoculated with	Amount, c.c.	No. Rabbits Injected	No. Rabbits Dead	No. Rabbits with Lesions	No. Positive Diagnoses	Incubation, Days	Period, Ave.	Per Cent
21	Filt. NASAL WASHINGS	0.5 -1.00	44	33	20	16	1-21	4	77
(One case suspicious. Nasal washings not sufficiently concentrated) (One case of relapse)									
28	C. S. F.	0.25-1.00	60	39	23	17	1-8	3	60
						Trans- missions			
9	Filt. Human Br.	0.5 -1.00	47	31	24	1-5	1-40	10	
3	Emul. Human Br.	0.5 -1.00	17	14	9	1-5	2-28	5	
DETAILS OF HUMAN BRAIN INOCULATIONS SINCE LAST REPORT									
Filtrates									
Virus 4a	Glycerolated	0.5 -1.00	2	2	1	1	40	..	50
Virus 4b	Glycerolated	0.5 -1.00	4	2	2	2	2-10	7	50
Virus 10a	Glycerolated	0.5 -1.00	3	2	1	2	19	..	33
Animal injected in first transmission died same day. Filtrate of this brain brought second animal down in 19 days. First animal apparently acted as host.									
Virus 10b	Glycerolated	0.5 -1.00	4	2	2	1	10	10	50
(Only one transmission owing to contamination of virus)									
Virus D	Filt. Saline Em.	0.5 -1.00	10	9	7	4	1-25	7	70
(Virus preserved in saline in refrigerator for 6 months)									
Virus L-	Glycerolated	0.25-1.00	12	10	8	5	1-30	9	66
Emulsions									
Virus L-	Glycerolated	0.25-1.00	11	11	7	5	2-28	5	64

of *Infectious Diseases*, September, 1920. In connection with our animal experiments, we wish to bring out that we have not only produced typical lesions in animals with cultures derived from virus of various kinds, but we have also been



FIG. 31.—Rabbit brain. Section of midbrain inoculated intravenously with organism (Loewe and Strauss).

able in many instances to recover the organism from the brains of animals so injected and also to produce lesions in animals injected in the same manner with control cultures.

Immunological studies are now in progress. These include complement fixation studies with both bacterial and virus

antigens, and neutralization experiments. Neutralization of both virus and culture by means of convalescent serum from cases of epidemic encephalitis has been successful. Both natural and acquired immunity in animals were demon-

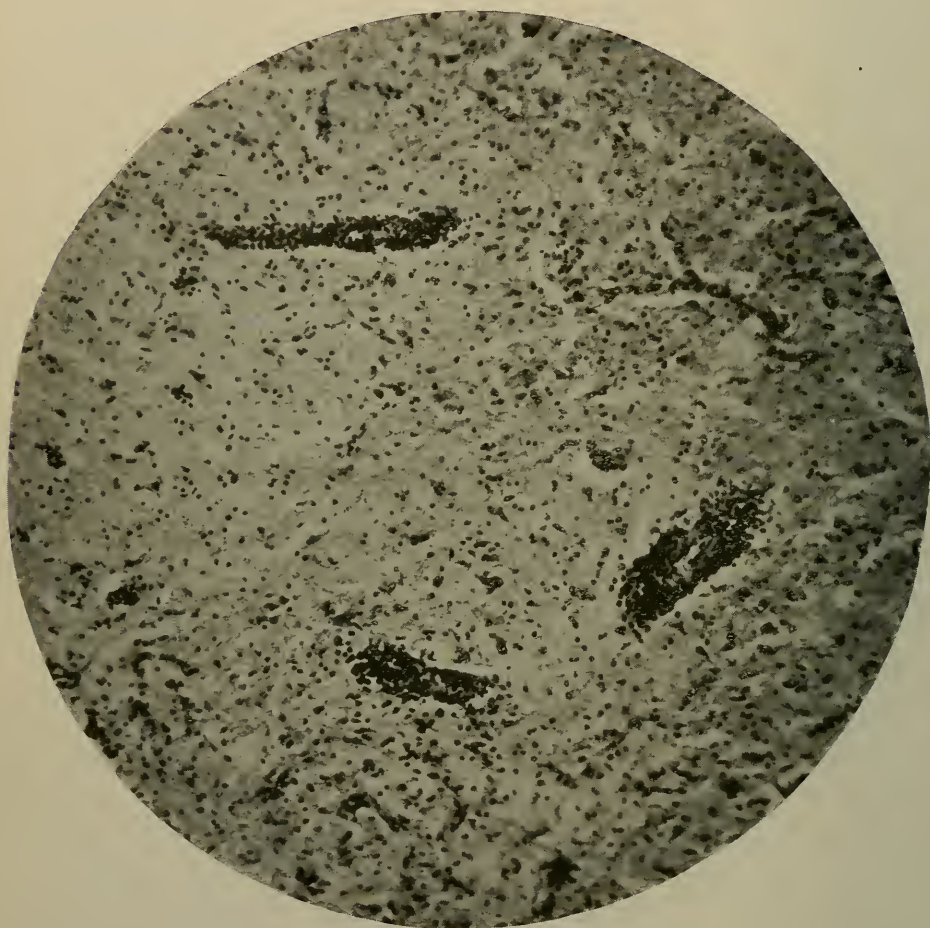


FIG. 32.—Rabbit. Section of spinal cord inoculated intravenously with organism. Same animal as that pictured in Fig. 31 (Loewe and Strauss).

strated. A peculiar phenomenon is chain formation when organisms are grown in convalescent serum, analogous to the so-called Pfaundler phenomenon with typhoid bacilli.

From the experimental work outlined above we wish to state that epidemic encephalitis is due to a living specific

infectious agent, different from that of poliomyelitis. This stand recently has been indorsed by both Levaditi and Harvier, and McIntosh and Turnbull.

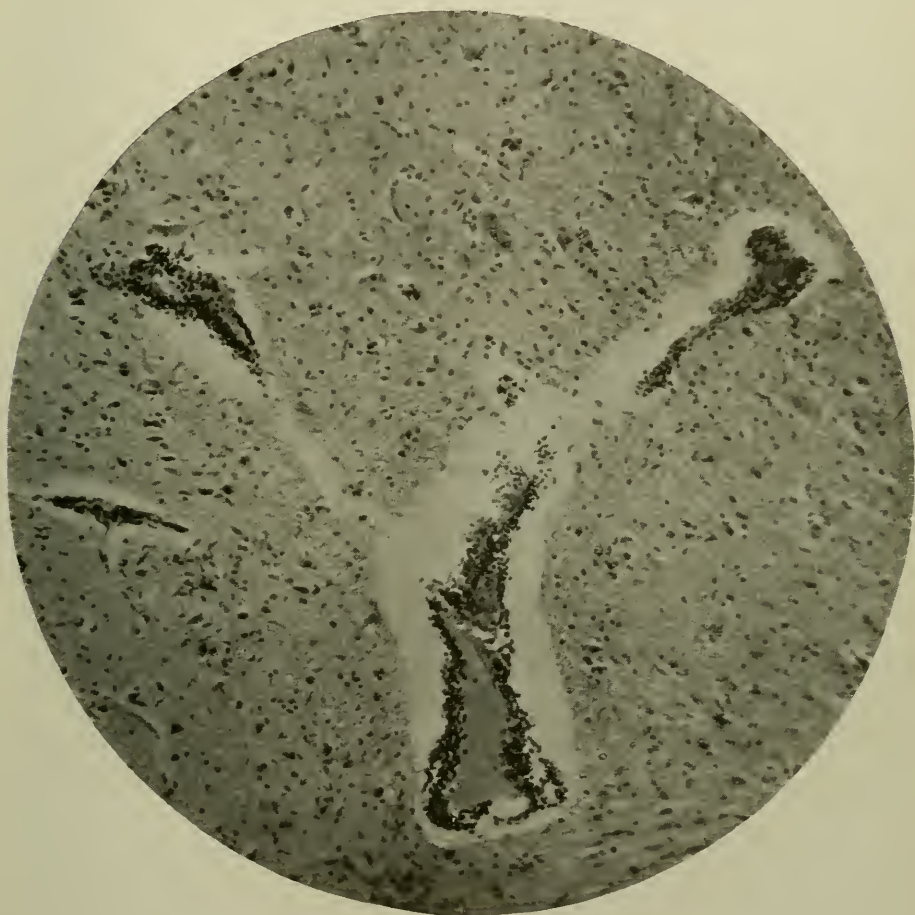


FIG. 33.—Monkey brain. Section of midbrain inoculated intracranially with organism (Loewe and Strauss).

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CULTIVATION OF THE VIRUS (ISRAEL STRAUSS). The criticism has been made that experimental inoculations with foreign material have produced lesions in rabbits. The foreign material which we have used, as shown in Dr. Loewe's paper, has consisted largely in filtrates; at times in emulsions and at other times in cultures. This is not foreign material in the sense in which pathologists use the term. The amount used is very small. The filtrates are nothing but filtrates of saline solution. The emulsion, of course, is a foreign substance inoculated into an animal, but you will note that in many instances we used controls—that is, we inoculated emulsions from the brains of individuals dying from other diseases, and never once in our experience did we find any lesion in these rabbits.

We have also inoculated the spinal fluids of cases suffering from diseases other than epidemic encephalitis, and again never once in all the rabbits we have used have we ever found any lesion. We have also used the nasal mucous membranes—filtrates of people suffering from diseases other than encephalitis, and again never found a lesion. The rabbit has been found to have diseases, especially diseases of the vessels similar to arteriosclerosis, which has negatived the work done in the production of arteriosclerosis in rabbits, but I know of no other lesion of any importance that has been found by experimental workers in rabbits, especially when using careful methods, which is like that produced by our inoculations.

When we presented this paper before the Society of Pathologists of New York City, not a single individual among



FIG. 34. Rabbit brain. Cortex of cerebrum showing focal infiltration with round cells in proximity to vessel showing mononuclear cell infiltration of the adventitia. Rabbit injected with same inoculum as animal pictured in Figs. 29 and 30.

the highly trained technical men present made any objection on this basis. In his discussion of our paper before the Academy of Medicine in May, Dr. Flexner who had failed to reproduce the disease in monkeys or rabbits described some inoculations made with a view of determining whether a lesion similar to encephalitis could be produced in a rabbit by using other organisms. He succeeded in producing a perivascular infiltration, by the use of an attenuated streptococcus viridans, but he admitted at that time that the lesions produced by us could not have been produced by a streptococcus viridans because we were competent enough in our bacteriological methods to have isolated a streptococcus viridans had such an organism been present in any of our fluids.

Levaditi and Harvier have produced in rabbits the typical lesions of encephalitis lethargica by inoculating rabbits with emulsions from the human brain. They have found that they could inoculate a monkey with the "virus fixe" obtained from the rabbit inoculations. They also succeeded in producing the disease in guinea-pigs, and what is of great importance when you consider this question of foreign material, they had produced the disease in rabbits by inoculating a rabbit in the sciatic nerve with the virus fixe and also by intraocular inoculation. They have confirmed our work in transmitting the virus from the nasal pharyngeal mucous membrane of human beings into rabbits, and they found out, as we had found out, that not only was the nasal mucous membrane infective for rabbits but the virus could be recovered in the nasal mucous membrane of rabbits that had been infected intracranially; in other words, that this was both the method of ingress and also of egress. They had also preserved the virus in the testicle of a rabbit for a number of days and they found, interestingly enough, that the retina of animals was also infectious.

Their conclusions were that this was a filtrable virus to be preserved in glycerine and was effective for both rabbits and monkeys, and can be rendered a virus fixe by repeated

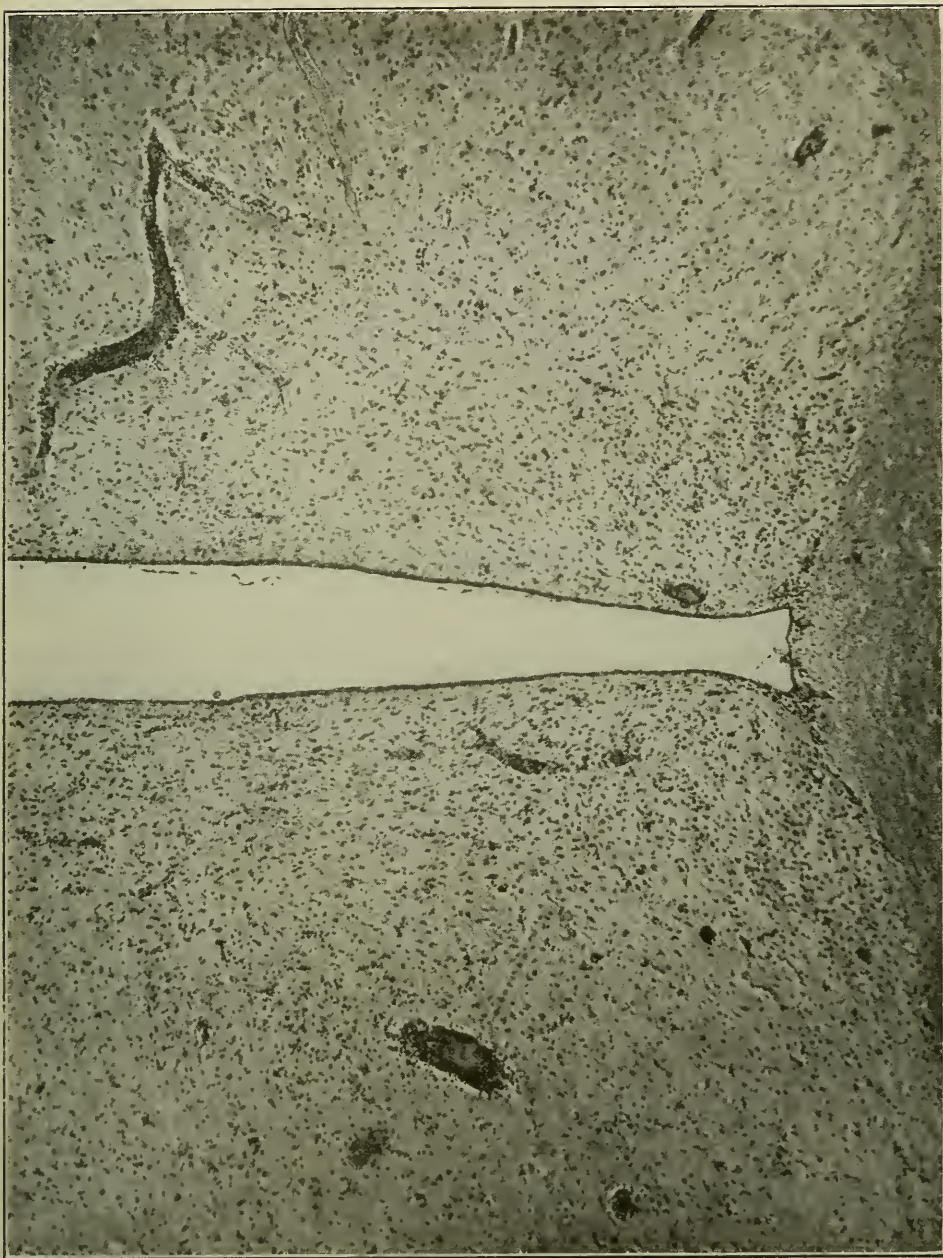


FIG. 35. Rabbit brain. Mononuclear cell infiltration of the parenchyma and of the adventitia of vessels in the basilar ganglia. Animal injected with Berkeley filtrate derived from nasopharyngeal mucous membrane of animal pictured in Figs. 29 and 30.

inoculations. In a personal comment by Levaditi he stated that his cultural work had not been extensive enough to give any results, and furthermore that he was having trouble with the serum which he was using. It may interest you to know that he sent us his virus and that we have cultivated the organism out of his virus and have it now in the fourth generation.

In England, Mackintosh and Turnbull have succeeded in producing the disease in a monkey by intracranial inoculations of the emulsion of the human brain, and also, again of importance regarding this criticism regarding the use of foreign material, by inoculation of a monkey intraperitoneally. In both cases their monkeys came down with lesions which McIntosh and Turnbull describe as characteristic pathologically.

Lastly, McIntosh alone has recently published an article in which he states that he has produced the disease in a series of rabbits and also a monkey, and, interestingly enough, also describes the characteristic lesion in a monkey which developed a spontaneous infection. The monkey having been in contact with the monkey which he had inoculated, came down at a period of incubation comparable to the period of incubation of the monkey inoculated.

There is as yet no confirmation of our work on the organism. We are dealing here with a new field of bacteriology, the field of filtrable organisms. Some years ago Foster isolated a filtrable organism from cases of common colds, and in Foster's article there is a footnote which is of a great deal of significance. He states that he attempted to do this work after reading Noguchi's description of his method, but he found he was unable to isolate the organism. He went to the Rockefeller Institute, and he states that in order to do work of this kind one has to study under the master himself, because the work is so difficult technically and is open to so many pitfalls that it is only by personal instruction, he thought, that one can acquire the method. His work so far as I know has not been confirmed.

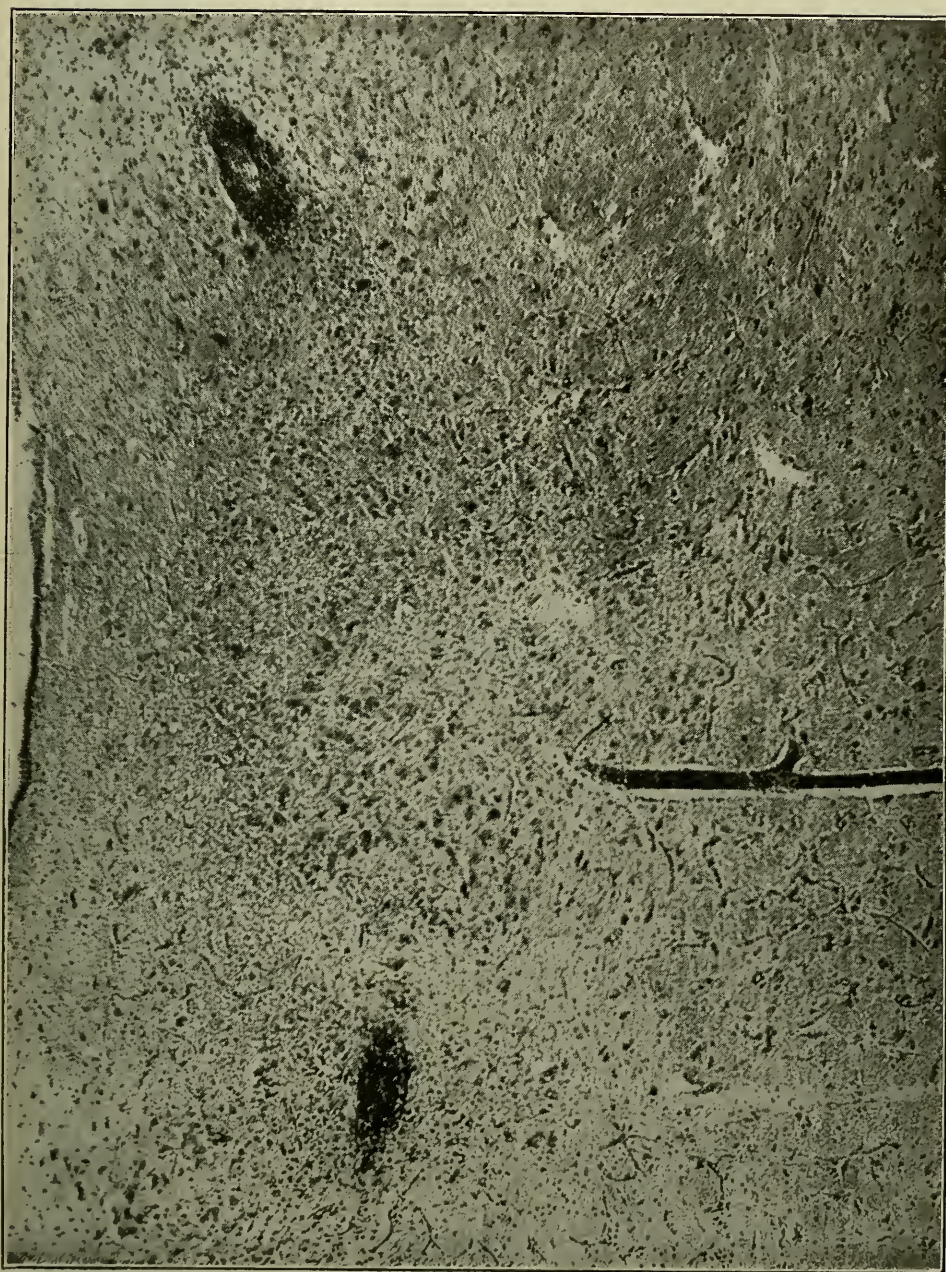


FIG. 36. Rabbit brain. Area of midbrain showing perivascular infiltration. Animal injected with cerebrospinal fluid from a human case.

The next piece of work on filtrable viruses is that of Flexner and Noguchi, who have isolated an organism from cases of poliomyelitis. The confirmation of their work has as yet not been general. Yet we personally believe that the organism isolated by Flexner and Noguchi is the etiological agent of poliomyelitis.

It is interesting to note that Bradford and Wilson in their studies of infective encephalitis during the war probably had the virus and isolated it. Then they made cultural studies which Arkwright criticised because he found that the organisms were not in pure culture, and they admit in the Arkwright article that they were probably wrong in assuming that they had the organism in pure culture. We believe ourselves that they probably did have the organism; but, as Arkwright had proved, it was not in pure culture. They made this error very likely because of their unfamiliarity with the method.

Our work is the latest that has been done in the study of filtrable organisms. We are indebted extremely to Noguchi for having shown us the way and the method. The finding of this organism does not in itself mean as much to us as does the fact that we feel that we have in our work placed upon record for bacteriologists and pathologists for the first time completely the fact that there is a filtrable organism as a cause of disease.

The following questions, submitted to Drs. Loewe and Strauss before the Commission, together with the answers to them, are here reported *verbatim*.

DR. DANA: Will you be good enough to tell us or explain the reasons why Dr. Amoss and his group of workers did not get the same results as you did?

DR. LOEWE: His results are practically as inexplicable to me as to the gentlemen gathered here. I can merely say that in order to straighten out this difficulty an invitation was extended to Dr. Amoss to come up and work with us. He found it difficult to do this,

so we attempted to compromise by having him run duplicate experiments with our materials and with our filters and by having us to run duplicate experiments with his filters and his materials. In other words, we feel that his negative results may be due to failure to obtain the same amount or the same quality of materials that we have obtained, or we feel that he may have used a certain type of filter which we have not used. I feel that is the only explanation, and we would welcome Dr. Amoss coming up and working with us in order to straighten out the difficulty.

I may say that our animal experimentation numerically far exceeds his, so far as he cited it at the Academy of Medicine, and in all our inoculations we were aware of a 50 per cent immunity in rabbits, and we therefore used series of animals. We did not spare animals or spare materials. I do not think he had as many autopsies as we were fortunate to have. We had twenty-four, and as I said, we used over 600 rabbits and over 40 monkeys.

DR. SACHS: May I ask you to make some statement as to whether in your own experiments you have had any distinct failures and what the proportion of failures has been?

DR. LOEWE: I believe I mentioned that with every individual material inoculated we had so many positives and the remainder were negative. That varied with the different materials. In spinal fluids our inoculations were less than with nasal washings; with the brain they were less than with nasal washings, etc., and our cultural work proportionately.

DR. DANA: I am requested to ask what the difference is between the filter used by Dr. Amoss and by yourself. Do you know?

DR. LOEWE: I haven't any idea. In the beginning of the work I can merely say that we used a Berkefeld filter, but owing to the exigencies of the war, etc., we were unable to obtain the original Berkefeld filters later and we therefore used the domestic filters which we found satisfactory in a certain proportion of cases. We tested our filters carefully and discarded as much as 75 or 80 per cent of a given lot; before using a filter we were careful enough to test it out against the usual test organisms, and when they proved satisfactory to us we continued our experiments with those particular filters.

DR. TAYLOR: In what respect do you regard your organism as related to that of poliomyelitis? In the first place do you regard it as a specific organism or possibly as a different strain of the organism which presumably is the cause of infantile paralysis?

DR. LOEWE: We feel that the two diseases are distinct; just as there are groups of streptococci and pneumococci there are groups of organisms with different pathogenic characteristics. Culturally they are the same or practically the same, with slight differences which do not amount to much because we may find differences in cultural biological characteristics in a given organism and given strain at different times; but from our neutralization experiments we feel that the organism is specific. In other words, we have formed neutralization experiments with convalescent serum with both virus and culture, and we have protected animals by bringing the culture in contact with the convalescent serum for a certain length of time, injecting new animals, of course, and controlling it with injections of virus alone into the animals.

DR. TAYLOR: In your animals you not infrequently got lesions pathological to a certain extent and clinical signs which were analogous to infantile paralysis, didn't you?

DR. LOEWE: We got paralytic conditions.

DR. DANA: Was there any other case of apparent contagion? With regard to the contagiousness of the disease, you spoke as though one animal appeared to acquire the disease through contact with another, did you not?

DR. LOEWE: I believe Dr. Strauss mentioned the literature on that subject. We personally are not prepared to say that we have had any contact infections, but McIntosh describes a distinct contact infection, an infection which can only be ascribed to contact. In other words, the incubation period between the original inoculation and symptoms in one monkey and the symptoms in another monkey one would only ascribe to contact infection. I may say that all our experimental animals were isolated and kept in cages apart from normal animals, and there was no possibility of contact infection.

DR. NEUSTAEDTER: In what percentage of cases in monkeys did you have anterior horn lesions and in what percentage purely cerebral lesions?

DR. LOEWE: I cannot state the percentages. I can only recall two animals in which we got distinct lesions in the spinal cord, and even in those two animals there was no destruction of the anterior horn cells. As I say we are carrying on a minute comparative study of these animals which we are prepared to publish at some

subsequent date, but I feel sure we will not find the lesions of poliomyelitis in our experimental animals. Incidentally, I do not believe anybody has been able to produce the lesions of poliomyelitis in rabbits, as we pointed out. Marks, of course, has inoculated rabbits with poliomyelitis virus and subsequently brought down monkeys with them, but he himself claims, and rightly so, that the rabbit in his case merely acted as a host for the virus.

DR. STRAUSS: I want to call attention to one part of the work which Dr. Loewe mentioned and which is new and extremely significant. It may have escaped the attention of the Commission. That is the intravenous inoculation of this organism and the remarkable thing that it showed a selective affinity for the brain. These animals died after an intravenous inoculation. Now regarding this contact infection which Dr. Dana has asked about, Dr. Loewe has forgotten to mention something of which we are not exactly certain as yet. As we stated, we have kept our animals isolated with one exception. The sheep that died after intravenous inoculation was in the same pen with another sheep, and this second sheep has died, and our autopsy of this second sheep showed us nothing but a marked degeneration of the liver. The brain, however, has not been studied, so we are not yet prepared to state whether this second sheep has come down with encephalitis or not. We are anxiously awaiting the results of the culture studies of that sheep's brain because it may be that we likewise have got a contact infection. That is the only instance in which two animals were kept close beside each other. While this one was dying, the other sheep was beside it and the food was not separated. We are not yet prepared to say but what we may have an example of contact infection there.

DR. THALHIMER: It is my privilege to present to you some cultural and experimental studies of epidemic encephalitis. The main value which these results might have is that they are confirmatory of the work which have been reported by Dr. Loewe and Dr. Strauss. From the central nervous system material from 4 fatal cases of epidemic encephalitis has been available—spinal fluids from 3 cases which I have completed the study of myself, and from a fourth spinal fluid the results of which I heard by letter yesterday. Two of these fatal cases were of the fulminating type that died within thirty-six hours. One of the spinal fluids was from one of the fulminating cases; one was from a convalescent case of

the lethargic type—a nurse who was sick in a hospital in Chicago. The third spinal fluid was from a lethargic soldier at the Waukesha Hospital for Soldiers near Milwaukee. Virus from the central nervous system from these 14 cases has been injected into rabbits and has produced the disease—has produced the microscopic lesions of the disease, and this virus has been carried through ten series of animals.

From the central nervous system an organism has been recovered and this organism is filtrable and has all the cultural and other characteristics which have been described and has been carried through from twelve to fourteen generations. Rabbits inoculated intracranially with these cultures have come down with the disease. The organism has been recovered from their brain. A large number of animals inoculated with the virus at various stages of its passage have been cultivated and the organism has also been recovered from their brains. More recently guinea-pigs have been used—inoculated intracranially both with virus and cultures—have come down with the disease, have shown a microscopic lesion and the organism has been recovered again from their brains.

The fourth spinal fluid which I just heard from was obtained from rather a peculiar case. The animal was inoculated intracranially and died fourteen days after inoculation, and I have also heard that sections of the brain showed a typical microscopical lesion. In other words, the results reported by Drs. Loewe and Strauss of the filtrable virus obtainable from the central nervous system of spinal fluid have been confirmed in the laboratory at Columbia Hospital, Milwaukee. A filtrable microorganism has been grown from this material on the perfected medium of Noguchi. This organism has been injected into animals, has reproduced the disease, microscopic lesions, and this organism has again been recovered from the brains of these animals.

IMMUNOLOGICAL DISTINCTIONS OF ENCEPHALITIS AND POLIOMYELITIS (HAROLD L. AMOSS). The means of distinguishing epidemic poliomyelitis and lethargic encephalitis, which has not yet been applied, relates to the point whether the serum of convalescent cases of lethargic encephalitis can neutralize the virus of poliomyelitis. This fact is readily determined experimentally by the method described by

Amoss and Eberson.¹ The principle of the test lies in the power of a neutralizing serum, when administered intraspinally, to prevent the development of poliomyelitis in the monkey following the intravenous injection of a large dose of the virus.

The blood serum of 4 cases of lethargic cencephalitis was used in the test, one from a patient convalescent in the fifth week of the disease, the second in the fourth month, the third in the fifth month, and the fourth fifteen months after the attack. The tests were controlled by two experiments in which the same procedure was followed, except that one monkey received intraspinal injections of normal human serum and the other intraspinal injections of poliomyelitic serum from a monkey which had had experimental poliomyelitis nine months before and recovered with residual paralyses.

The virus of poliomyelitis used came from a strain which had been passed from monkey to monkey many times during the past nine years and which, between passages, had been preserved in 50 per cent glycerol in the ice box. Before starting the tests, this virus was passed through three normal monkeys in order to determine its virulence.² The certain infecting dose for intracerebral injection was found to be 0.25 c.c. of a Berkefeld filtrate of a 5 per cent suspension of the nervous tissues containing the virus.

The infecting power of the virus when given intravenously is shown in the following preliminary experiment.

A monkey received at 5 p.m. an intraspinal injection of 2 c.c. of normal horse serum. The following morning 50 c.c. of a 5 per cent suspension of fresh virus were given intravenously. Five days later the animal was weak in both legs and excited. Both arms were paralyzed on the sixth day and the monkey died on the seventh day.

Autopsy. Microscopic lesions of experimental poliomyelitis were found.

¹Amoss, H. L., and Eberson, F. J. *Exper. M.*, 1918, xxvii, 309.

²All intracerebral inoculations were made under ether anaesthesia.

In making suspensions for intravenous injections the tissues used must be fresh. Accordingly, a monkey prostrate from an intracerebral injection of 0.5 c.c. of a suspension of the virus six days before, was killed with ether and autopsied at once. A 5 per cent suspension of the cord and medulla was prepared for immediate injection.

Series I

Experiment 1. Macacus rhesus A. Normal human serum control. March 11, 1920, 5.50 p.m., injected intraspinally 2 c.c. of fresh normal human serum. March 12, 2.30 p.m., injected intravenously 50 c.c. of a 5 per cent suspension of fresh poliomyelitis nervous tissue. 2.50 p.m., intraspinal injection of 2 c.c. of fresh normal human serum. The intraspinal injection of 2 c.c. of normal human serum was repeated daily for three days. March 18th, excited; slight head tremor and left facial paralysis. March 19th, prostrate. March 20th, etherized when moribund.

Autopsy. Microscopic lesions of experimental poliomyelitis.

Experiment 2. Macacus rhesus B. Immune poliomyelitic serum. March 11, 1920, 6 p.m., injected intraspinally 2 c.c. of serum from a monkey which had had experimental poliomyelitis nine months before and had recovered with residual paralyses. March 12, 3 p.m., injected intravenously 50 c.c. of virus suspension. 3.25 p.m., intraspinal injection of 2 c.c. of poliomyelitic immune monkey serum. The intraspinal injections of 2 c.c. of immune monkey serum were repeated daily for three days. The monkey remained well.

Experiment 3. Macacus rhesus C. Serum from convalescent case of lethargic encephalitis. March 11, 1920, 6.05 p.m., injected intraspinally 2 c.c. of serum from Case 1, aged thirty-one years, who was in the fifth week of well-defined lethargic encephalitis with general disturbance of the functions of the central nervous system and involvement of third and seventh cranial nerves. March 12th, 3.30 p.m., intravenous injection of 50 c.c. of virus suspension. 3.35 p.m., intraspinal injection of 2 c.c. of encephalitis serum from Case 1. The intraspinal injection of the encephalitic serum was repeated daily for three days. March 17th. Animal slow and weak. March 18th. Found dead at 9 a.m.

Autopsy. Microscopic lesions of experimental poliomyelitis.

Experiment 4. Macacus rhesus D. Serum from convalescent case of lethargic encephalitis. Mar. 11, 1920, 6.10 p.m., injected intraspinally 2 c.c. of serum from Case 2, aged thirty-four years, three months after definite attack of lethargic encephalitis in which there was general disturbance of the function of the central nervous system, involving the third and seventh cranial nerves and spinal motor roots. March 12th, 4 p.m., intravenous injection of 50 c.c. of virus suspension. 5 p.m., injected intraspinally 2 c.c. of convalescent encephalitis serum from Case 2. The intraspinal injection of 2 c.c. of encephalitic serum was repeated daily for three days. March 18th. Excited and ataxic. March 19th. Prostrate. March 20th. Etherized when moribund.

Autopsy. Microscopic lesions of experimental poliomyelitis.

Series 2

The second series of tests carried out at a different time was controlled by an experiment in which normal human serum was used for the intraspinal injections as in Experiment 1. The procedure in this series was the same as in Series 1, except that normal horse serum was used for the preparatory intraspinal injection given the day before the intravenous injection of virus. The same strain of virus employed in Series 1 was again tested for infecting power and used in this series.

Experiment 5. Macacus rhesus E. Normal human serum control. May 18, 1920, 4.10 p.m., injected intraspinally 2 c.c. of normal horse serum. May 19th, 12 m., intravenous injection of 50 c.c. of virus suspension. 12.25 p.m., injected intraspinally 2 c.c. of normal human serum. The intraspinal injection of normal human serum was repeated daily for 3 days. May 23rd. Monkey excited; both legs weak. May 24th, complete paralysis of both legs and right facial paralysis. May 25th. Died.

Autopsy. Microscopic lesions of experimental poliomyelitis.

Experiment 6. Macacus rhesus F. Serum from case of lethargic encephalitis. May 18, 1920, 4 p.m., injected intraspinally 2 c.c. of normal horse serum. May 19th, 11.30 a.m., intravenous injection of 50 c.c. of virus suspension. 11.55 a.m., intraspinal injection of 2 c.c. of serum from Case 3, aged twenty-eight years,

taken four and a half months after acute onset of lethargic encephalitis. The patient's illness began with dizziness, disturbance of vision, vomiting and fever, and he gradually became stuporous. Later paralyses referable to the seventh and spinal nerves appeared. The intraspinal injection into the monkey of the convalescent serum was repeated daily for three days. May 26th, monkey had paralysis of both arms and shoulder muscles. May 27th. Died.

Autopsy. Microscopic lesions of experimental poliomyelitis.

Experiment 7. *Macacus rhesus* G. Serum from case of lethargic encephalitis. May 18, 1920, 4.20 p.m., injected intraspinally 2 c.c. of normal horse serum. May 19th, 11 a.m., intravenous injection of 50 c.c. of virus suspension. 11.25 a.m., injected intraspinally 2 c.c. of serum from Case 4, aged twenty-four years, who had developed lethargic encephalitis fifteen months before and was still under observation with residual ptosis and partial paralysis of left side of face and left leg. The intraspinal injection into the monkey of the convalescent encephalitis serum was repeated daily for three days. May 24th, monkey had double ptosis. May 25th, shoulder muscles paralyzed; arms and legs very weak; head tremor; animal almost prostrate. May 26th. Died.

Autopsy. Microscopic lesions of experimental poliomyelitis.

The experiments here reported show, the two diseases can be distinguished through the power of blood serum under certain circumstances to neutralize the virus of poliomyelitis. The blood serum of convalescent cases of poliomyelitis whether in man or monkey possesses this neutralizing power, while the blood serum of recently convalescent cases of epidemic encephalitis is devoid of it.

On the basis of the distinguishing characters described, it is regarded as desirable at the present time to hold epidemic poliomyelitis and epidemic encephalitis as integrally distinct affections. The latter also may be infectious, yet the main lesions of poliomyelitis are present in the spinal cord, and of epidemic encephalitis in the midbrain.

The following questions submitted to Dr. Amoss before the Commission, together with the answers to them, are here reported *verbatim*.

DR. TILNEY: Would you be good enough to discuss a little more in detail why you selected the *in vivo* method in preference to the *in vitro*?

DR. AMOSS: The *in vitro* method depends upon the following experiment. You take 2 c.c. of the serum and add to it 2' *m.l.d.*'s of your virus; let it set in the incubator for two hours and overnight in the ice box, and inject the whole mixture in the monkey. If you will take a series of these—I have done I think 20 at one time, using the same serum—say, using 5 monkeys on one serum, you will find that some of the monkeys come down and some do not. Whether it is a question of hydrogen-ion concentration or whether it is a question of the variation in the immune bodies, one can't tell. So they are not clear-cut experiments. Some of them will come down and some will not. Another thing—normal human serum will sometimes neutralize *in vitro*, but normal human serum never neutralizes *in vivo*.

DR. BARKER: Keeping in mind the possibility that the virus of encephalitis might be a modification of the virus of poliomyelitis—the modification going so far as to involve also production of diphenyl bodies—is there anything known in immunology that would correspond to that possibility?

DR. AMOSS: There is only one analogy which occurs to me now. I do not know if there are any others. If you take a pneumococcus type 2, pneumococcus type 2 serum will agglutinate pneumococcus type 2 in the sub-groups A and B. Pneumococcus type 2-A will not agglutinate a type 2 but will agglutinate only type 2-A, and so monotypical type 2-B will agglutinate only type 2-B and will not agglutinate type 2-A or type 2. That is the only group. It may be that it is perfectly possible from that analogy that encephalitis might be the more inclusive from an etiological standpoint and that poliomyelitis might correspond to type 2-A or type 2-B but I do not believe it.

DR. TIMME: Dr. Thalhimer, would you like to put any questions to Dr. Amoss regarding the various discrepancies or findings in your respective work.

DR. THALHIMER: I do not think there are any questions that can be put at this particular time. The state of affairs is that there were simply two series of experiments done—on the one hand in a number of different laboratories with positive results with microscopic lesions and with the recovery of an organism, and a

series of experiments by Dr. Amoss of the Rockefeller Institute with negative results. I do not think there are any questions coming up between the two at present. I think the only thing that is indicated is that with this divergence a suggestion is in order that these two series of workers in some way come together and compare their technique and compare their results, and see if there might not be between them in a technical way some differences which can be eradicated. The work has got to stand or fall as it becomes more generally verified or not, and I think that the immediate thing to be done—being as there are sufficient number of people interested in this disease to come to these meetings—is to ask Dr. Amos if he will attempt to come together and go over this with Dr. Strauss or myself, and see if we cannot evolve something which is worth while in an experimental manner.

DR. SACHS: May I ask Dr. Thalhimier whether he knows if encephalitis immunity studies have begun?

DR. THALHIMER: Yes, the immunity studies have been begun at Mt. Sinai Hospital.

DR. SACHS: There is a question handed in here: Is it true that the disease complex of poliomyelitis cannot be reproduced in rabbits while an encephalitic process of encephalitis lethargica can be produced in some animals.

DR. AMOSS: It is a question whether or not poliomyelitis has been transmitted to rabbits. Rosenauer and Caven thought that they were able to transmit the disease to rabbits, and Marks about eight years ago thought he had been able to transmit poliomyelitis to rabbits. However, in view of the findings in normal rabbits which I reported a while ago, and in view of the experiments by Clark and some of the rest of us at the Rockefeller Institute, I do not believe that anybody has ever transmitted poliomyelitis to rabbits. We have taken young rabbits, as young as you can inject them and let them live, and we have gone further and given them massive doses of x-ray so as to reduce their lymphocytes. Now we know that if you ray monkeys so that the lymphocytic curve comes down about 200 to 600 round cells per cubic millimeter, those animals are much more susceptible to poliomyelitis, but not so rabbits. So I think it is not established that rabbits will take experimental poliomyelitis.

IMMUNOLOGICAL STUDIES OF EPIDEMIC ENCEPHALITIS AND POLIOMYELITIS (MARCUS NEUSTAEDTER, JOHN H. LARKIN

AND E. J. BANZHAF). It is a well established fact, as was shown by Flexner and Lewis, Netter and Levaditi, Roemer, and Anderson and Frost, that serum of patients recovered from poliomyelitis neutralizes virus of poliomyelitis in vitro and also protects monkeys from the disease when injected with such a mixture. It is also known that normal human serum does not as a rule neutralize the virus.

Following are the protocols of experiments:

Experiment 1. March 6, 1920. Maccacus A was injected intracerebrally with 0.5 c.c. of a mixture of poliomyelitis virus and serum of patient Miriam S., aet. 16 years, three months after recovery from lethargic encephalitis, prepared in the following manner:

0.125 c.c. of a 5 per cent suspension of brain and cord of a monkey that died of poliomyelitis, obtained through the courtesy of Dr. Amoss from the Rockefeller Institute, were mixed with 1.25 serum of the above patient and incubated at 37° for two hours and kept in the refrigerator for twenty hours.

Result. The animal remained well without any visible ill effects until April 21st, when it was found dead. The autopsy showed that the cause of death was tuberculosis.

Control. Maccacus B was injected in the same manner with 0.5 c.c. of a mixture of the same virus and in the same proportion with normal adult serum prepared as above.

Result. The animal became paralyzed on the eighth day in the right upper and lower extremities but survived until October when it was anesthetized and autopsied.

Experiment 2. May 18, 1920. Maccacus E was injected intracerebrally with 1 c.c. of a mixture of equal parts of a 5 per cent suspension of Rockefeller Institute poliomyelitis virus and serum of patient Dawe J., aet. 30, recovered from lethargic encephalitis since February 20, 1920. This mixture was incubated at 37° for 1 hour and 20 minutes and kept on ice for 19½ hours.

Result. The animal remained perfectly well until August 25th.

Control. Maccacus D was injected in the same manner with 1 c.c. of a mixture of equal parts of the above virus and normal adult serum prepared as above.

Result. May 24th, the animal found ill sitting in a corner of the cage; May 25th paralysis in all four extremities and muscles of the

neck; shallow respiration. Anesthetized and autopsied. Macroscopical and microscopical changes characteristic of poliomyelitis.

Experiment 3. June 22, 1920. Maccacus F injected intraspinally with 4 c.c. of a mixture of equal parts of a $2\frac{1}{2}$ per cent suspension of virus of monkey D and serum of Dr. G., aet. 55 years, suspected of having had lethargic encephalitis, still having a paralysis of facial nerve with complete reaction of degeneration. This mixture had been incubated at 37° for 2 hours and kept on ice for 22 hours.

Result. The animal remained well up to November 5th.

Control. Maccacus G was injected as above with 4 c.c. of the same virus mixed with equal parts of normal NaCl solution, and incubated as above.

Result. June 28th, the animal ill, refuses food.

June 29th paralyzed in all four extremities and muscles of the neck. Anesthetized and autopsied. Macroscopical and microscopical changes typical.

Experiment 4. October 8, 1920. Maccacus K was injected intracerebrally with 1.5 c.c. of a mixture of equal parts of an 8 per cent suspension of poliomyelitis virus of Maccacus E and serum of patient from Dr. Foster Kennedy's service in Bellevue Hospital, who had recovered from lethargic encephalitis. The mixture was incubated for 2 hours at 37° and kept in the refrigerator for 22 hours.

Result. The animal suffered no ill effects and is well today.

Control. Maccacus L was injected with 1.5 c.c. of a mixture of equal parts of the above virus suspension and serum of a normal adult, prepared as above.

Result. October 14th, animal very ill; left upper extremity parietic; October 16th., both hind limbs parietic; October 19th, animal recovered from pareses and is well today.

Experiment 5. October 28, 1920. Maccacus M injected intracerebrally with 1.5 c.c. of a mixture of equal parts of a 10 per cent suspension of poliomyelitis virus of Maccacus E and serum of patient Mary S., aet. 16 years, from the service of Dr. Foster Kennedy at Bellevue Hospital, and originally observed and described by Dr. Tilney as Case IV in his book, "Epidemic Encephalitis." The patient is at present in the neurological service of the City Hospital. This mixture was incubated at 37° for 2 hours and kept on ice for 22 hours.

Result. The animal remained well.

COMPARATIVE RESULTS IN NEUTRALIZATION TESTS OF POLIOMYELITIS
VIRUS WITH SERUM OF PATIENTS CONVALESCENT FROM
POLIOMYELITIS AND LETHARGIC ENCEPHALITIS

	<i>Monkeys Injected</i>	<i>Result</i>
Flexner and Lewis	5 poliomyelitis virus + human con- valescent poliomyelitis serum 3 poliomyelitis virus + human sus- pected poliomyelitis serum 7 and 9 injections of poliomyelitis virus + normal human serum of adults and children	4 protected 1 paralyzed, living 1 protected 2 paralyzed and died 3 paralyzed and died 3 protected 1 died, no paralysis and no poliomyelitis lesions
Netter and Levaditti	4 poliomyelitis virus + human con- valescent poliomyelitis serum 1 control, poliomyelitis virus + nor- mal salt solution 3 poliomyelitis virus + human con- valescent poliomyelitis serum 1 control, poliomyelitis virus + nor- mal human serum	4 protected 1 paralyzed and died 3 protected 1 paralyzed and died
Roemer	3 poliomyelitis virus + human con- valescent poliomyelitis serum 1 control, poliomyelitis virus + nor- mal salt solution 3 poliomyelitis virus + human con- valescent poliomyelitis serum 1 control, poliomyelitis virus + nor- mal new born infant serum, intra- cerebrally, and 5 c.c. pure virus in- traperitoneally 2 controls, poliomyelitis virus + nor- mal new born infant serum	3 protected 1 paralyzed and died 3 protected 1 paralyzed and died 1 slightly paretic, recov- ered 1 paralyzed and died
Anderson and Frost	1 poliomyelitis virus + human con- valescent poliomyelitis serum 10 poliomyelitis virus + human sus- pected poliomyelitis serum 10 controls, poliomyelitis virus + nor- mal human serum	1 protected 7 protected 1 paralyzed and died 2 paralyzed, survived 3 protected 7 paralyzed
Authors' cases	5 poliomyelitis virus + human con- valescent lethargic encephalitis serum 4 controls, poliomyelitis virus + nor- mal human adult serum 1 control, poliomyelitis virus + nor- mal salt solution	5 protected 1 paralyzed and dying 1 paralyzed, survived 2 paretic, recovered 1 paralyzed and dying

All sera were Wassermann negative.

Control. Maccacus N was injected in the same manner with 1.5 c.c. of a mixture of the above virus suspension and equal parts of serum of an eighteen year old laboratory helper, who claimed never to have been ill.

Result. November 2nd, the animal was ill and paretic in the right upper extremity and showed also a slight hypotonia in the right lower extremity. The same condition prevails today.

Experiment 6. In order to establish whether the protection afforded the animals was due to the use of the convalescent encephalitis serum, Maccacus E was injected intracerebrally with 1 c.c. of a 5 per cent suspension of brain and cord of Maccacus G on August 25th, about three months after the initial injection.

Result. August 31th, the animal was found paralyzed in all extremities and dying. Macroscopic and microscopic changes were characteristic of poliomyelitis.

All sera used proved Wassermann negative and the serum of a different person was used as a control in each experiment.

Five monkeys were completely protected from poliomyelitis by sera of patients convalescent from 4 undoubted cases and one suspected case of lethargic encephalitis.

The results compare favorably with the results of other investigators in the neutralization experiments of poliomyelitis virus and convalescent human poliomyelitis sera.

It is concluded from these facts that there is a close point of contact between lethargic encephalitis and poliomyelitis.

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The following questions, submitted to Dr. Neustadter before the Commission, together with the answers to them, are here reported *verbatim*.

DR. DANA: Why will you not draw some conclusions?

DR. NEUSTAEDTER: I believe that before we could draw any definite conclusions two other things ought to be done, which I am in process of working on. One is to test out the spinal fluids of so-called lethargic patients with poliomyelitis virus for complement fixation. I have been doing that for the last few months in frank cases but I have not sufficient number to draw any conclusions. Results are so far very encouraging. Another experiment that I want to make and that I spoke to Dr. Strauss about some time ago was the antipoliomyelitis horse serum that neutralizes virus in much greater proportions. That is, the poliomyelitis horse serum neutralizes poliomyelitis virus in proportions of one to two; two of virus to one serum. I want to cross the experiment and try the virus of encephalitis, as they have, and neutralize that with our serum which we know neutralizes in every instance, without exception, poliomyelitis virus. When I have those three factors together I believe it will give us greater encouragement to draw conclusions than at the present time.

DR. DANA: As I understand it, you state that the serum from convalescent encephalitis cases neutralized the poliomyelitic monkey. Do you infer from that that the diseases must be very closely identical?

DR. NEUSTAEDTER: I would say there is a close contact between the two. I would not say anything further than that. I believe there is a close contact between the two; whether it is another phase or what it is, I am not prepared to say.

DR. DANA: May there not be many other infectious diseases the convalescent serum from which might do the same?

DR. NEUSTAEDTER: That has been tried, as far as I know, again and again, and never succeeded.

DR. DANA: You could say that some other convalescent serum than that of encephalitis or poliomyelitis neutralizes the virus of poliomyelitis, couldn't you?

DR. NEUSTAEDTER: Other infectious diseases such as measles, scarlet fever, etc., have been tried and did not do it, but we do know that from the results of other investigators the serum of so-called normal people has neutralized the virus, and in my experiments here two controls became ill but recovered. So you see normal human sera also contain some principles evidently that protect the monkey to a certain extent.

DR. PATRICK: In the case of the physician, how long had this physician had the facial palsy before you saw him?

DR. NEUSTAEDTER: A week.

PHYSIOLOGIC KNOWLEDGE AS RELATED TO SYNDROMES OF EPIDEMIC ENCEPHALITIS (FRANK H. PIKE). On our hypothesis of localization, a lesion of any particular group of cells should produce a definite effect. One asks whether or not these lesions in encephalitis are of the nature of deficiency lesions, the effects being such as one might get from excision of definite parts of the nervous system without inflammatory conditions or irritating conditions afterward, or whether these are of the nature of irritative lesions.

Some years ago Stewart and Pike in animal experimentation tied off the blood-vessels to the brain for a short period of time, say eight to ten minutes, and observed the effects. There were convulsions and rigidity which might persist for three or four days. In case of recovery these would gradually pass off. These cases were done aseptically and conditions verified at autopsy. At that time at least no changes were found which suggested encephalitis or meningitis. In these cases as was shown afterward there was always a chromatolysis. The cells were diffusely stained and this change was found at times to persist for days after recovery.

The question was raised as to whether the chromatolysis itself might have been sufficient to account for the rigidity, and perhaps for the convulsions. It seems to be pretty sure that some agents at least which act injuriously upon nerve cells or nerve fibers will increase their excitability. It is known, of course, that there is an action current produced at every beat of the heart, yet the phrenic nerve on the left side runs right in contact with the pericardium. There is no twitching of the diaphragm ordinarily. The threshold of stimulation of this phrenic nerve is too high to be excited by the action current of the heart. Yet by decreasing the oxygen supply, by decreasing the blood supply of this phrenic nerve, it is perfectly possible to demonstrate that the

diaphragm on the left side twitches at each beat of the heart. It seems, therefore, pretty sure that there are conditions which will increase the actual excitability of nerve fibres and also of nerve cells.

Now, until we know more of the effects of toxins upon nerve cells, one must, if he keeps within the limits of veracity, be extremely brief. Many of the claims that have been made for a specific action of toxins upon various parts of the nervous system are not very well founded. The effects, or the supposed effects, of pneumonia toxin, which is probably the most prominent, and perhaps also diphtheria toxin has been shown to lie in the end organs perhaps more than in the central system.

One point perhaps is the relation of the ectasis of the blood to the lethargy. Experimentally, of course, we can reduce the blood supply to the brain to almost any desired degree. It is perfectly possible to tie up both carotid and both vertebral arteries in a cat or a dog, and most dogs will live after that, but during the period of associated lethargy we often find that there are convulsions. We find great respiratory disturbances as well, and within the last two years we have found that in every case of this kind which we tried experimentally there are characteristic changes in the carbon dioxide and oxygen concentration of the blood. Just as soon as one reduces the volume of blood flowing through the brain, just so soon will one reduce the concentration of carbon dioxide in the blood and increase the concentration of oxygen.

From this point of view then, if ectasis is the only thing concerned in the production of lethargy, one would expect certain respiratory changes, and also certain circulatory changes. When the nerve cells are uninjured and one simply reduces the blood supply, there is a prompt rise in the systemic blood-pressure, and we have shown also that the usual relation exemplified by Marey's law in the high blood-pressure and low heart rate may be departed from here. We get a dissociation of response. We may get a rapid heart rate along with a high blood-pressure. Stasis may in part

account for this lethargy, particularly in view of the perivascular infiltration which has been described, but one should be inclined to attribute a part of this lethargy at least to some other cause.

The muscular rigidity in some cases at least departs somewhat from the conditions we get experimentally. Sherrington and others have shown that in lesions of the cerebrum we get a typical rigidity of the muscles, a decerebrate rigidity. This affects the extensor muscles. In some cases of epidemic encephalitis there is a pretty general rigidity of extensors as well as flexors. This would seem to differentiate the effects in encephalitis, so far as our experimental knowledge goes, from the effects of a pure cortical lesion.

It has been somewhat difficult for one to see just how a lesion of the endocrine system could produce such opposite effects as have been described. One can hardly see, for instance, how a low blood-pressure and profuse sweating might be due to the action of adrenalin since the action of the sweat gland is due to the sympathetic nervous system. It has been shown experimentally, as it had previously been postulated clinically, that there is a cortical mechanism for the secretion of sweat. One would like to know whether in these cases in which profuse sweating has been observed the lesions seem to be more of the cortical type or whether they were confined to the region of the aqueduct, as seems to be the rule. We are inclined to think that we have an irritative process here as exemplified by the muscle tonus, and by certain of the other disturbances, namely, that of the sweat glands.

One or two observations which have been made on animals might be mentioned. A dog developed the disease known as distemper among dogs, but there was a recovery. There was a twitching of all four limbs persisting even during sleep at times. This continued for about twenty-five months after the attack. There was a similar dog up in the Harvard Laboratory where there was this same twitching of the muscles, but it was more severe. Experiments were done to

see where some of these movements came from. The first thing was the exposure of the lumbar cord and the sections of the dorsal roots of the spinal nerves on one side. If these things were due to afferent impulses a section of the dorsal roots should have some effect. Perhaps the twitchings were somewhat decreased for a week or two, but they returned again, and people who saw the dog and who did not know on which side the nerve roots had been sectioned were unable to tell any particular difference in the two sides. Following that was extirpated a motor area on one side. If this was due to cortical irritation, extirpation of the motor area should have some effect. The dog died of hemorrhage in a few hours, but in the time the dog survived, one couldn't see that there was any marked effect on the twitchings on the two sides. It seemed to be distinctly due to something outside of the cerebral cortex.

The following questions, submitted to Professor F. H. Pike before the Commission, together with the answers to them, are here reported *verbatim*.

DR. SACHS: I would like to ask Dr. Pike whether the movements of that dog resembled in any way such movements as we have described here as following encephalitis? Were they of the choreatic or myoclonic type?

DR. PIKE: I think from the description I have heard, and from some cases I have seen, they are very much like those. They are very general; they involve even the jaw muscles. You could hear the teeth click. And there was some respiratory change. At times the breath would come in gasps. At first there was some weakness of the muscles of the limbs. The dog was unable to go up or down stairs unassisted, but that passed off in time. The dog became able to draw a sled with two boys on it. I couldn't notice any difference in the general intelligence or general habits.

DR. BARKER: Dr. Hohman mentioned a case in which there was rhythmical myoclonia. The rate of the myoclonic contractions was in a definite ratio with the respiratory rate. I think he referred to some work of Dr. Pike's suggesting that this meant that rhythmical myoclonia must have an origin in the medulla oblongata. Can you give us any data on that?

DR. PIKE: It is only in cases of considerable respiratory difficulty that I have observed any movements outside of the respiratory movements under experimental conditions. Many of these symptoms which have been described, seem to me to point to an involvement of the medulla. In experimental work on the cerebellum or any region around the fourth ventricle one must be extremely cautious to avoid pressure or irritation, even though it be slight, of the floor of the fourth ventricle. I am in doubt yet sometimes as to the actual effects of cerebellar lesions. I am not sure that they are uncomplemented by effects on the floor of the fourth ventricle. In cases of increased excitability of nerve cells which one might possibly have in this disease of encephalitis, there is of course a possibility that some of these muscular movements might arise during respiration and be associated with respiratory movements. I don't think we have any definite proof.

CONCLUSIONS OF THE COMMISSION

The Commission feels that the evidence submitted before it on the bacteriology and pathogenesis of epidemic encephalitis, together with the incidental additions brought out in the questionnaire, while not entirely conclusive as to the specific nature of epidemic encephalitis and its productive organism, yet is of the greatest weight. The work of Drs. Loewe and Strauss, confirmed by Dr. Thalheimer and by many European investigators, notably Levaditi and Harvier, McIntosh and Turnbull, and Ottolenghi, D'Antona and Tonietti, seems to the Commission to merit high commendation as having established apparently the closest relationship between organism and disease. The negative attitude was not one which pointed out errors of technique or fault in material or error in conclusion, but only inability to reproduce the same effect. And there is, it seems to the Commission, room for this discrepancy in the lack of using material obtained by different methods, and by the use of presumably different filters. The commendable attitude of the investigators in desiring to remove their differences by the respective use of each others' material and technical apparatus, lends hope that unity of conclusion will soon eventuate.

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